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International Agency for Research on Cancer

ATTRIBUTABLE CAUSES OF CANCER IN FRANCE IN THE YEAR 2000

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This report is co-authored by:

The International Agency for Research on Cancer (IARC)
P. Autier, P. Boffetta, M. Boniol, P. Boyle (Co-Chair), J. Ferlay

The Académie Nationale de Médecine
A. Aurengo, R. Masse, G. de Thé

The Académie des Sciences
R. Monier, M. Tubiana (Co-Chair), A.J. Valleron

The Fédération Nationale des Centres de Lutte Contre le Cancer (FNCLCC)
C. Hill

In partnership with the Institut National du Cancer (INCa)
L. Borella, D. Maraninchi

Institutions consulted:
Institut de Veille Sanitaire (InVS)

Reviewers:
France,

For the entire report: J. Benichou (Université de Rouen), J. Estève (Hospices Civils de Lyon).

For specific parts of the report: P. Bougnoux (Institut National de la Santé et de la Recherche Médicale [INSERM]) for the sub-section on nutrition, M. Goldberg (INSERM) for the section on occupational exposure, G. Orth (Institut Pasteur) for the section on infectious agents, H. Rochefort (INSERM) and C. Sureau (Académie Nationale de Médecine) for the section on hormone replacement therapy and oral contraceptives, H. Sancho-Garnier (Université de Montpellier) for the section on ultraviolet light, D. Zmirou-Navier (INSERM) for the sub-section on air pollution.

International,

For the entire report: J. Peto (London School of Hygiene and Tropical Medicine, London, United Kingdom), J. Siemiatycki (University of Montreal, Montreal, Canada).

For specific parts of the report: H. zur Hausen (Deutschen Krebsforschungszentrums [DKFZ], Heidelberg, Germany) for the section on infectious agents.

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Correspondence:
Prof. Peter Boyle, International Agency for Research on Cancer, 150 cours Albert Thomas, 69372 Lyon, France.
Email: director@iarc.fr

Prof. Maurice Tubiana, Académie Nationale de Médecine, 16 rue Bonaparte, 75005 Paris, France.
Email: maurice.tubiana@biomedicale.univ-paris5.fr

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Introduction

Section A1: Objectives and methodology

1. Background

Many factors, whether genetic, or related to lifestyle or the environment, have been identified over the past 50 years as being associated with cancer occurrence.

About 2 to 4% of all cancers seem to have a genetic origin, i.e., gene defects known to be associated with these cancers can be transmitted from parents to their offspring. Moreover, genetic polymorphisms and epigenetic phenomena may enhance or reduce the risk associated with endogenous or exogenous carcinogenic factors. During the past two decades, it has been assumed that most cancers are due to lifestyle or to environmental risk factors. Very many epidemiological studies have been reported, but they are often contradictory or of debatable value because of methodological problems or lack of sufficient statistical power. Hence, their results have to be critically reviewed. In parallel, our understanding of carcinogenesis has markedly progressed, but the data are still insufficient to fully establish the different steps of carcinogenesis and the interaction between the various endogenous or exogenous factors. In many fields, further research is clearly required. Nevertheless, the strategy of cancer prevention must be based on the latest estimates of the relative weight of the various lifestyle and environmental risk factors. The aim of this report is to estimate the proportions of cancer attributable to such risk factors and also to evaluate the weight of each factor in the burden of cancer. This report distinguishes solid data from those which are still dubious or controversial; the former may be considered and taken into account in decision-making in cancer prevention and for prioritizing public health and research efforts.

Discussions about the roles of lifestyle and of the environment in cancer are often hindered by confusion over the meaning of the term “environment”, which is variably interpreted to encompass quite different types of factor ranging from pollutants to behaviours. Also, this term (or its equivalent) is given different meanings in different languages. In this report, we use the term “environment” as meaning “environmental pollutants”, an expression that includes pollutants of water, air, soil and food.

The first estimate of the relative importance of genetic and environmental factors in the global burden of cancer was made by Richard Doll and Richard Peto (1981), based on US cancer mortality data. Since then, only a few studies have tried to estimate the relative importance of cancer risk factors (see Section E2, General Discussion for a review). In 1981, a number of risk factors were still unknown and good qualitative and quantitative information on exposure of populations to risk factors was rare. Many nations have now entered the era of “information societies.” In this respect, in 2007, we have more information on exposure patterns and thus should be able to estimate better the burden of cancer that can be attributed to known causes, and to provide an evaluation of their relative importance.

At the beginning of 2005, the IARC created a “think-tank” on this topic, with the aim of developing methods for first obtaining estimates of the proportions of cancers attributable to known causes and second estimating the number of cancers that could be avoidable. In July 2005, a workshop at IARC brought together cancer epidemiologists who concluded that studies on attributable causes of cancer should start by examining a few selected countries in the five continents.

In September 2005, the French Académie Nationale de Médecine and the French Académie

des Sciences proposed to IARC to collaborate on a study on attributable causes of cancer in France. The present report is the product of this collaboration.

2. Objectives

The purpose of this report is to provide an assessment of the number of cancer cases and cancer deaths in France in the year 2000 attributable to factors of demonstrated carcinogenicity or with a demonstrated association with carcinogenic processes.

Ionizing radiation is a well established risk factor for cancer at many sites. There is fairly good knowledge of the cancer risk due to exposure to moderate and high doses of ionizing irradiation. However, the vast majority of exposure to ionizing radiation in France consists of low and very low doses. The specific effects of low-dose ionizing radiation on cancer risk are still controversial and difficult to quantify properly. Therefore, it was decided not to present data on cancer cases and deaths possibly attributable to radiation for the whole country. Following the same argument, no estimate was made for residential exposure to radon decay products. Section D1 on ionizing radiation addresses this issue in more detail.

For a number of factors, the evidence of a role in human cancer is suggestive but not demonstrated; these factors are reviewed in a separate section of the report (Section D3), but no estimates of attributable fraction are provided for them.

3. Methodology

Estimation of attributable causes of cancers was performed by calculating the proportions of specific cancers occurring in France in 2000 attributable to specific risk factors. The proportion of cancers in the total population that can be attributed to a risk factor is called the *attributable fraction* (AF) (Armitage and Berry, 1987) and is expressed as a percentage.

For cancer risk factors that can be avoided or completely suppressed, at least in theory, the most straightforward way to estimate the attributable fraction is to calculate the fraction of all cases (exposed and unexposed) that would not have occurred if exposure had not occurred (Rothman and Greenland, 1998). For this approach, the alternative scenario to current exposure is the absence of exposure.

For cancer risk factors that cannot be completely avoided or suppressed, a suitable approach consists of estimating the avoidable fraction of cancer, that is the fraction of cancer that would not occur if an alternative scenario of attainable exposure level or exposure intensity were considered (Murray and Lopez, 1999).

Most estimates of AF in this report are based on the scenario of *no exposure*, as this does not require assumption of minimal levels of exposures to carcinogens that would represent realistic targets for the French population. However, “total absence” is not a realistic alternative scenario for several risk factors, notably the number of children a women has (for breast and ovarian cancer). For such factors, it was deemed best to choose an alternative scenario that was historically realistic, i.e., exposure levels that had existed in France in the past.

4. Incidence data

France does not have nationwide cancer registration that would allow the monitoring of cancer incidence at the national level. There are, however, registries operating in several departments, some of which focus on specific cancers. For the year 2000, estimates of cancer incidence in France were obtained from a study that estimated the nationwide burden of cancer for the period 1997–2000 (Remontet et al., 2002). This report presented estimates of the incidence of cancer at the main sites for the period 1978–2000, using incidence data from departmental registries and the national mortality data for the period 1978–1997. Cancer incidence in France in 2000 was derived by age–cohort modelling of (i) incidence from cancer registries, (ii) mortality in populations covered by cancer registries, and (iii) incidence-to-mortality ratios in populations covered by cancer registries. This model was applied to predicted national mortality for the year 2000 so as to estimate the national cancer incidence in 2000.

Some specific cancer sites were not reported by Remontet et al. (2002):

(1) For **sinonasal cancer** incidence (ICD 10: C30, C31), we calculated the ratio of incidence of sinonasal to lung cancer in nine cancer registries that record sinonasal cancers (Parkin et al., 2002: Bas-Rhin, Calvados, Doubs, Haut-Rhin, Hérault, Isère, Manche, Somme and Tarn) and applied that ratio (0.019 for

men and 0.033 for women) to lung cancer incidence in France, which yielded estimates for sinonasal cancer incidence for France of 453 cases for men and 151 cases for women. Mortality data were available directly from CepiDc data: 99 deaths for men and 42 deaths for women.

(2) For the incidence of **pharynx cancer** (ICD 10: C09–14), we estimated the proportion of pharynx cancer among oral cavity and pharynx cancers (ICD 10: C00–14) in French registries (Parkin et al., 2002: Bas-Rhin, Calvados, Doubs, Isère, Somme and Tarn). The proportion of pharynx cancer among oral cavity and pharynx cancers was 57% for men and 35% for women. We applied this proportion to data reported by Remontet et al. (2002) for oral cavity and pharynx combined, and obtained figures of 7396 cases of pharynx cancer for men and 833 cases for women. Mortality data were available directly from CepiDc data: 2558 deaths for men and 312 deaths for women.

(3) For **colon cancer** (ICD 10: C18), we estimated the proportion of colon cancer among colorectal cancers (ICD 10: C18–21) in French registries (Parkin et al., 2002: Bas-Rhin, Calvados, Doubs, Isère, Somme and Tarn). We estimated that colon cancer represents 57% of colorectal cancers for men and 63% for women. We applied these proportions to data reported by Remontet et al. (2002) for colon and rectum combined, and obtained figures of 11 132 cases of colon cancer for men and 10 606 cases for women. Mortality data were available directly from CepiDc data: 6092 deaths for men and 5719 deaths for women.

(4) For **adenocarcinoma of the oesophagus**, we had recourse to a European study that used data from the cancer registries of Bas-Rhin and Calvados and reported separately the incidence of oesophageal adenocarcinoma (Botterweck et al., 2000). Proportions of adenocarcinoma were estimated as 17.6% of all oesophageal cancers in males, and 34.7% in females. We applied these proportions for incidence and mortality data of oesophagus (ICD 10: C15), which led to estimates of 711 cases for men and 322 for women. The corresponding figures for mortality were 612 deaths for men and 241 for women.

5. Mortality data

Mortality data were provided directly by the Institut National de la Santé et de la Recherche Médicale, Centre d'Epidémiologie sur les Causes Médicales de Décès (INSERM-CepiDC) for the year 2000 by five-year age groups and by sex for each ICD 10 code (International Classification of Disease, 10th revision).

Fifty-six per cent of all uterus cancers were coded as "uterus not further specified" (ICD 10 code C55). Mortality data for cancers of the cervix and corpus uteri would be underestimated unless this "not specified" category is redistributed among the two sites. Therefore, we estimated for each age group the proportion of deaths due to cervix or corpus uteri cancer (ICD 10 codes C53 or C54). We applied these proportions to the "not classified" uterine cancer deaths and reallocated these to either cervix uteri cancer or corpus uteri cancer.

6. Issues in the classification of diseases and causes of death

Remontet and co-workers (2002) compiled cancer incidence and mortality data using the 9th revision of the International Classification of Disease (ICD 9), and estimated cancer incidence in 2000 using projections of mortality for 2000. INSERM mortality data for 2000 were classified using the 10th revision of the ICD. Differences between the two ICD classifications could have affected the mortality estimates, notably for uterus and prostate cancer, multiple myeloma and leukaemia. However, Pavillon and co-workers (2005) estimated that differences in the two classification systems did not induce discrepancies greater than 10% in causes of deaths. Therefore, we did not correct the incidence data for 2000 compiled by Remontet and co-workers to match the INSERM mortality data for 2000. Table A1.1 summarizes cancer incidence and mortality in France in the year 2000 for males and females.

7. Risk factors for cancer in France

Risk factors considered in this report were those for which there is evidence for a causal association with cancer.

The first type of risk factor considered comprises those agents classified by the IARC as Group 1 carcinogens, i.e., agents for which there is *sufficient evidence of carcinogenicity* in humans. Exceptionally, an agent may be placed in this category when evidence of carcinogenicity in humans is less than *sufficient* but there is *sufficient evidence of carcinogenicity* in experimental animals and strong evidence in exposed humans that the agent acts through a relevant mechanism of carcinogenicity[1]. Since 1971, the International Agency for Research on Cancer has provided evaluations of the carcinogenic potential of substances based on epidemiological and biological evidence. The term "substance" encompasses single physical, chemical, or biological agents, and mixtures of physical chemical, biological and physical agents, and also places or circumstances concentrating still unknown carcinogenic agents. Table A1.2 summarizes the list of carcinogenic agents considered in this report.

The second type of risk factor includes individual conditions known to be causally associated with cancer occurrence. These factors are not evaluated in IARC Monographs but some have been evaluated by working groups convened by the IARC. An IARC working group came to the conclusion that there was sufficient evidence in humans for a cancer-preventive effect of avoidance of weight gain (IARC, 2002), and thus this report estimates AFs associated with overweight and obesity. The same IARC working group reported that there was sufficient evidence for a protective effect of physical activity on the risk of breast cancer and colon cancer (IARC, 2002).

Reproductive factors (e.g., number of children, age at first birth, duration of breastfeeding) have never been evaluated by an IARC working group. However, a large body of evidence supports strong associations between reproductive factors and breast and ovarian cancer (CGHFBC, 2001). We therefore included these factors in this analysis.

A number of IARC Group 1 carcinogens were not included in this report, either because exposure is very rare in France or because they are insignificant. For instance, parasitic infestation with *Schistosoma haematobium* (involved in bladder cancer) and *Opisthorchis viverrini* (involved in liver cholangiocarcinoma), and intake of nutrients such as aflatoxins (involved in liver adenocarcinoma) (see Section D2).

8. Prevalence of exposures in France

The burden of cancer observed in the year 2000 reflects past exposure to risk factors. Usually, exposure to a risk factor is spread over many years, and cancer may occur long after cessation of the exposure (e.g., lung cancer in ex-smokers, mesothelioma in retired shipbuilding workers). For most cancers and risk factors, the average latency between first exposure and diagnosis is about 15 years. Hence, for evaluating the burden of cancer in 2000, we took into account exposures that occurred in or around 1985.

Data on prevalence of exposure to risk factors in France were assembled by scrutinizing many different sources, publications, reports and relevant information publicly available on governmental organization web-sites.

The most representative exposure data for the population at risk came from population surveys that evaluated the prevalence of specific exposures in France, and were conducted using quota methods on age, sex and socioeconomic characteristics (e.g., INSEE surveys). For most exposures, however, prevalence surveys were not available for the year 1985, but only for other years. In this case, we calculated a linear interpolation of survey results that used a similar method for years before and after 1985, with weighting for sample sizes and, when relevant, for age and sex distribution. When similar surveys before and after 1985 were not available, we selected the best available survey describing the situation around 1985. When no survey was available, we used proportions of exposed subjects reported in observational studies conducted in France.

Attributable fraction is very sensitive to misclassification of subjects who could have been exposed (even minimally) as unexposed subjects (Wacholder et al., 1994). For instance, the error in an estimate of AF due to tobacco smoking is greater when occasional smokers are categorized as never-smokers than when they are included in the ever-smoker category. Therefore, the simplest and most robust method for estimating the attributable risk from several exposures is based on division of subjects into

[1] http://monographs.iarc.fr

two groups, a baseline consisting of those unexposed and a group including everyone who was exposed.

9. Calculation of the attributable fraction (AF)

The AF can be calculated as a function of the relative risk (RR) of cancer associated with exposure to a risk factor and the prevalence of exposure (P) of a population to that risk factor. This method was originally described by Levin (1953):

$$AF = \frac{P^* (RR-1)}{[P^* (RR-1)] + 1}$$

The relative risks we used were based on estimates from the most recent meta-analyses or from best estimates available in published literature.

When a risk factor was reported in the literature in multiple exposure categories (i.e., exposures classified in more than two categories), we used Levin's formula adapted by Hanley (2001). Because of the distributive properties of the AF, multi-level exposures could be reduced to a simple dichotomous situation (i.e., ever vs. never exposed) or to an average exposure of the whole population at risk when the relative risk was related to an exposure level greater or lower than a pre-determined level. These ways of grouping or averaging strata of exposure do not affect AF estimations (Hanley, 2001).

Data on exposure prevalence were sometimes available only as continuous variables. For these continuous-scale exposures, starting from relative risks estimated for several exposure categories, we derived the risk of cancer per unit increase in exposure (e.g., the increase in risk of oesophagus cancer per unit gram per day of alcohol consumption). Assuming a log-linear relationship between exposure and risk of cancer, we estimated the average risk for the whole French population using the average level of exposure of the whole population. This was done by applying the following formula:

$$Risk = Exp\,[Ln\ (\text{Risk per unit}) * \text{average level of exposure}]$$

Because this log-linear relationship supposes that each individual has experienced a similar average exposure, we can use the simplified Levin's formula for direct calculation of the AF:

$$AF = \frac{Risk - 1}{Risk}$$

This formula is valid when the risk of cancer per unit of exposure was estimated in a model using log transformation. This is the case for logistic regression or Poisson regression, which are models widely used in case–control and cohort studies respectively. We checked that the risks per unit we used were all based on models with a log transformation of the risk.

It should be stressed that the dose–effect relationship is in fact rarely linear (or log-linear) over the whole range of exposures, but this method is considered to be the best approximation available in this respect.

10. Sensitivity analysis

For exposures having a large impact on cancer burden, in order to check the robustness of AF with respect to latency time between exposure and cancer occurrence, we took different lag-times between first exposure and cancer diagnosis (10 and 20 years) when prevalence data were available for these periods.

When for a risk factor, the alternative hypothesis was not total absence of exposure, the sensitivity analysis was performed taking different alternative exposure scenarios.

A more comprehensive description of this sensitivity analysis is presented in Section C2.

References

Armitage P, Berry G. Statistical Methods in Medical Research, second ed., London, Blackwell Scientific Publications, 1987.

Botterweck AAM, Schouten LJ, Volovics A, et al. Trends in incidence of adenocarcinoma of the oesophagus and gastric cardia in ten European countries. Int J Epidemiol 2000;29:645–654.

CGHFBC. Collaborative Group on Hormonal Factors in Breast Cancer. Familial breast cancer: collaborative reanalysis of individual data from 52 epidemiological studies including 58 209 women with breast cancer and 101 986 women without the disease. Lancet 2001;358:1389–1399.

Doll R, Peto R. The causes of cancer: quantitative

estimates of avoidable risks of cancer in the United States today. J Natl Cancer Inst 1981;66:1191–1308.

Hanley JA. A heuristic approach to formulas for population attributable fraction. J Epidemiol Community Health 2001;55:508–514.

INSERM-CpiDC. www.cepidc.vesinet.inserm.fr, accessed in 2006.

International Agency for Research on Cancer. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Overall Evaluations of Carcinogenicity: An Updating of IARC Monographs Volumes 1 to 42, Supplement 7, Lyon, IARC, 1987.

International Agency for Research on Cancer. IARC Handbooks of Cancer Prevention, Vol. 6, Weight Control and Physical Activity. Lyon, IARC, 2002.

Levin ML. The occurrence of lung cancer in man. Acta Unio Int Contra Cancrum 1953;9:531–541.

Murray CJ, Lopez AD. On the comparable quantification of health risks: lessons from the global burden of disease study. Epidemiology 1999;10:594–605.

Parkin, DM, Whelan, SL, Ferlay, J et al. (eds). Cancer Incidence in Five Continents, Vol. VIII. Lyon, IARC, 2002.

Pavillon G, Boileau J, Renaud G, et al. Conséquences des changements de codage des causes médicales de décès sur les données nationales de mortalité en France, à partir de l'année 2000. Bull Epidémiol Hebdom 2005;4:13–16.

Remontet L, Buemi A, Velten M, et al. Evolution de l'incidence et de la mortalité par cancer en France de 1978 à 2000. Rapport FRANCIM, Hôpitaux de Lyon, INSERM, InVS, 2002.

Rothman KJ, Greenland S. Modern Epidemiology, second ed. Philadelphia: Lippincott-Raven, 1998.

Wacholder S, Benichou J, Heineman EF, et al. Attributable risk: advantages of a broad definition of exposure. Am J Epidemiol 1994;140:303–309.

Table A1.1 - Incidence of and mortality from cancer in France in 2000

		Incidence **				Mortality ***			
		Males		Females		Males		Females	
Site	**ICD 10**	**Number of cases**	**Rate***	**Number of cases**	**Rate***	**Number of cases**	**Rate***	**Number of cases**	**Rate***
Breast	C50	-	-	41845	138.5	-	-	10950	36.3
Central nervous system	C70-72	2697	9.5	2602	8.6	1609	5.6	1290	4.3
Cervix uteri	C54			3387	11.2	-	-	1463	4.8
Colon-rectum	C18-21	19431	68.1	16826	55.7	8345	29.3	7604	25.2
Corpus uteri	C53	-	-	5064	16.8	-	-	1360	4.5
Gallbladder	C23-24	815	2.9	1272	4.2	519	1.8	938	3.1
Hodgkin disease	C81	736	2.6	631	2.1	168	0.6	117	0.4
Kidney	C64	5306	18.6	2987	9.9	1888	6.6	1107	3.7
Larynx	C32	3865	13.6	361	1.2	1702	6.0	149	0.5
Leukaemia	C91-95	3609	12.7	2634	8.7	2694	9.4	2352	7.8
Liver	C22	5014	17.6	962	3.2	5019	17.6	1600	5.3
Lung	C33-34	23152	81.2	4591	15.2	20585	72.2	4246	14.1
Melanoma	C43	3066	10.8	4165	13.8	706	2.5	643	2.1
Mesothelioma	C45	671	2.4	200	0.7	606	2.1	162	0.5
Multiple myeloma	C88,C90	1942	6.8	1645	5.4	1352	4.7	1309	4.3
Non-Hodgkin lymphoma	C82-85,C96	5527	19.4	4381	14.5	2281	8.0	2185	7.2
Oesophagus	C15	4040	14.2	928	3.1	3477	12.2	695	2.3
Non-melanoma skin cancer	C44	-	-	-	-	212	0.7	211	0.7
Oral cavity and pharynx	C00-14	12990	45.6	2398	7.9	3911	13.7	732	2.4
Ovary	C56	-	-	4488	14.9	-	-	3210	10.6
Pancreas	C25	2701	9.5	2186	7.2	3631	12.7	3205	10.6
Prostate	C61	40309	141.4	-	-	9080	31.8	-	-
Stomach	C16	4520	15.9	2606	8.6	3156	11.1	2011	6.7
Thyroid	C73	821	2.9	2890	9.6	140	0.5	251	0.8
Urinary bladder	C67	8986	31.5	1785	5.9	3250	11.4	1007	3.3
Other		10827	38.0	6394	21.2	12406	43.5	8110	26.8
All cancers	**C00-97**	**161025**	**564.8**	**117228**	**388.1**	**86737**	**304.2**	**56907**	**188.4**

* Crude rate per 100 000 person years. ** From Remontet et al., 2002 *** From Inserm-CepiDC

Table A1.2 - Selected agents causally associated with cancer (IARC Group 1 carcinogens)

Agent	Risk factor	IARC Monograph volumes and year*	
Alcohol	Alcoholic beverages	Vol. 44	1988
Chronic infection	*Helicobacter pylori*	Vol. 61	1994
	Hepatitis B virus	Vol. 59	1994
	Hepatitis C virus	Vol. 59	1994
	Human papillomavirus	Vol. 64	1995
Hormonal therapy and oral contraceptives	Hormonal therapy Oral contraceptives	Vol. 72, 95 § Vol. 72, 95 §	1999, 2006 § 1999, 2006 §
Occupational exposures	Aromatic amines	Vol. 1 & 4, (7) †	1987
	Asbestos	Vol. 14, (7)	1987
	Benzene	Vol. 29, (7)	1987
	Boot and shoe manufacture and repair	Vol. 25, (7)	1987
	Cadmium	Vol. 58	1993
	Chromium (VI)	Vol. 49	1990
	Mineral oil	Vol. 33, (7)	1987
	Nickel	Vol. 49	1990
	Painters	Vol. 47	1989
	Polycyclic aromatic hydrocarbons (combustion fumes, tar, pitch)	Vol. 35, (7)	1987
	Radon decay products	Vol. 78	2001
	Rubber industry	Vol. 28, (7)	1987
	Silica	Vol. 68	1997
	Wood dust	Vol. 62	1995
Pollutants	Non-occupational exposure to asbestos	Vol. 14, (7)	1987
	Radon decay products	Vol. 78	2001
	Secondhand smoking	Vol. 83	2004
Radiation	Background exposure, terrestrial gamma and cosmic rays	Vol. 75	2000
	Medical diagnosis radiations	Vol. 75	2000
Solar radiation	Sun exposure	Vol. 55	1992
	UVA and psoralens	Vol. 24, (7)	1987
Tobacco	Tobacco smoking	Vol. 83	2004

*http://monographs.iarc.fr.
§ In press.
† (7) refers to the last update of evaluation reported in IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Overall Evaluations of Carcinogenicity: An Updating of IARC Monographs Volumes 1 to 42, Supplement 7, Lyon, 1987.

Section A2: Temporal trends in cancer incidence and mortality in France

This section examines temporal trends in cancer incidence and cancer mortality in France. It has been known for many years that incidence and mortality of most human cancers steeply increase with the ageing of populations. The worldwide phenomenon of population ageing is therefore, in most countries, the principal cause of the increasing number of cancer cases and cancer deaths over time. Population ageing is particularly significant in Europe and so most of the change in the numbers of patients diagnosed with or dying from cancer is due to the increasing number of people in older age strata.

We first examine the effects of population ageing on mortality trends. Next, we examine the residual incidence and mortality trends after the influence of ageing is removed by statistical adjustments. Finally, we examine the reasons other than ageing that are likely to underlie the observed changes in incidence and mortality of specific cancers.

1. Data on cancer incidence and mortality in France

For incidence, we combined the data from cancer registries that have reported since 1978 or 1979 and published data in the *Cancer Incidence in Five Continents* (CI5) series (Parkin et al., 2005); namely Bas-Rhin (1978–1997), Calvados (1978–1997; except for leukaemia, because of the incomplete reporting of the disease [see CI5 Vols. VII and VIII]), Doubs (1978–1997), and Isère (1979–1997). These registries cover only 5.6% of the French population, but provide data covering at least 20 years, which is a reasonable time window for appraisal of trends.

For mortality, we used data from Hill et al. (1989, 1990, 1991, 1993, 2001) for mortality before 1968, and the WHO mortality database for mortality between 1968 and 2003 (WHO, 2006). The French population figures for the period from 1968 to 2003 were those provided for 1 January of each year by the INSEE. All incidence and mortality rates have been standardized on age, using the standard World population defined by Segi (1960), and introduced in CI5 volume I by Doll et al. (1966).

2. Temporal trends in cancer incidence and mortality in France

Decrease in age-adjusted cancer mortality over time

Before looking at changes in any specific cancer, we examined how population increase and ageing have influenced cancer mortality in France. Table A2.1 shows that in a period of 35 years, from 1968 to 2003, the number of cancer deaths in France increased by 50% in men (from 58 914 to 88 201) and by 26% in women (from 46 865 to 59 033). However, the computations detailed in Table A2.1 show that the increase in the number of cancer deaths over time is entirely due to the increase in population size and to ageing.

Applying the cancer mortality rates observed in 1968 to the population of 2003 (the “expected deaths” in Table A2.1), we see that the numbers of cancer deaths observed in 2003 were 6.9% lower in French men and 18.9% lower in French women than if the 1968 rates were still valid in 2003. Hence, relative to 1968, the burden of cancer deaths in France has actually decreased by 6.9% in men and by 18.9% in women.

Age-adjusted cancer mortality is decreasing but age-adjusted cancer incidence is increasing

Figure A2.1 displays temporal trends in age-adjusted incidence in the four registries that had data from 1978 until 1997, and the age-adjusted mortality rates for the whole French population from 1950 until 2004.

The trends in cancer mortality rates observed in the four departments from which the incidence data originate were similar to those observed in the entire French population.

Most cancers that occurred in 1950, the year from which the earliest mortality data exist, were initiated in the 1930s, when a large part of the French population was living in rural areas, with low numbers of motorized vehicles and less chemical substances than after the Second World War.

Over a twenty-year period, cancer incidence rates have increased by 23% in men and by 20% in women. Because the rates in Figure A2.1 are adjusted for age, the increases in incidence are real, and not related to the ageing of the French population. In contrast, the cancer mortality rate in males reached a maximum around 1985 and decreased steadily thereafter, down to the level it was in the early 1950s.

To properly interpret the discrepancy between age-adjusted incidence and age-adjusted mortality trends, we need to examine the reasons for changes in trends for specific cancers.

3. Reasons for changes in incidence and mortality of specific cancers

Figures A2.2 to A2.8 display trends in age-adjusted incidence and mortality rates of the most common and selected less common cancers in French men (Figures A2.2, A2.3, A2.4) and women (Figures A2.5, A2.6, A2.7, A2.8). Figure A2.9 displays trends in mortality from cancer in children and adolescents. Cancer incidence data in children could not be used because French childhood cancer registries include data covering different periods of time, which made difficult the production of temporal trends.

Reasons for changes in cancer incidence and mortality other than ageing, described by Doll and Peto (1981), are summarized below:

1. Administrative and demographic reasons:
   a. Changes in histological classification;
   b. Changes in disease classification;
   c. Changes in completeness of registration;
   d. Changes in populations: changes in denominators for calculation of rates, or significant immigration of populations having different cancer epidemiological profiles;
2. Changes in competing causes of death;
3. Changes in disease diagnosis;
4. Changes in earlier detection and screening practices;
5. Changes in exposure to risk or to protective factor(s) associated with cancer occurrence:
   a. Changes in nature of risk factors (qualitative change);
   b. Changes in exposure to risk factors (quantitative change).
6. For mortality: changes in efficacy of treatments and availability of efficient treatments.

The remainder of this section examines the influence of these various reasons on trends in cancer incidence and mortality in France associated with factors other than ageing. As a note of caution, the reasons outlined below by no means explain the totality of the observed time-trends, but the available data suggest that they have played an important role in changes in incidence or in mortality rates.

In cancers with high fatality rates, for which no efficient treatment yet exists, changes in incidence will be paralleled by equivalent changes in mortality, but with a time lag that is proportional to the average survival of these patients.

Incidence of a cancer may increase while mortality remains stable or decreases. Persistence over time of a discrepancy between increasing age-adjusted incidence and stable age-adjusted mortality rates is usually a result of increasing diagnosis of cancers with low malignant potential, some of which would probably never have surfaced as clinical cancers. Such increased detection of slow-progressing, non-aggressive cancers will not affect mortality unless the increased detection includes diagnosis at an earlier stage of cancers that would have been life-threatening if diagnosed later. Cancer screening activities may affect mortality only if the latter condition is true.

A discrepancy between incidence and mortality trends may also be due to an increase in the incidence of cancer, including cancers at an advanced stage, due to changing prevalence of risk factors in the population while efficient treatment is available to limit cancer mortality. When efficient treatment exists, these two situations can be distinguished by looking at trends in incidence of cancer by stage at diagnosis, or by other indicators of cancer progression, such as tumour size, lymph node involvement, tumour differentiation or biomarkers of aggressiveness.

Unfortunately, only very few registries record these parameters of cancer progression.

(1) Changes due to administrative reasons

Part of the change in incidence and mortality from haemato-lymphatic cancers probably results from changes in classification. For instance, some leukaemias are increasingly considered as sub-types of non-Hodgkin lymphoma (NHL). In addition, some haematological disturbances are now considered as cancer when previously they were not, such as some mild forms of NHL. The increase in multiple myeloma is probably due to better diagnosis and changes in the histological classification of sub-clinical haematological disturbances, mainly in the elderly.

The increase in bladder cancer incidence is not paralleled by a similar increase in mortality. Bladder cancer incidence is subject to great variability due to inclusion of pre-cancerous lesions in registry files. Earlier detection may also play a role (e.g., cystoscopic examinations).

(2) Changes due to competing causes of death

Competing causes of death refers to the decrease in one cause of death that leaves the road open for other causes of death, that may or may not be associated with the same risk factor(s). For instance, primary liver cancer in France is often associated with cirrhosis, a disease mostly due to high alcohol consumption. The latter is far more common in men than in women (see Section B2). It is hypothesized that part of the increase in the incidence of primary liver cancer observed in populations unexposed to aflatoxin and in which the incidence of viral hepatitis infection has not increased is due to more effective treatment of liver cirrhosis. As a consequence of greater survival of patients with cirrhosis, the later development of liver cancer would become more likely (Tubiana et Hill, 2004).

Prolongation of life expectancy has given time to lung cancer to emerge in workers exposed to silicosis, who would previously have died from obstructive chronic bronchitis. Similarly, primary prevention efforts and the availability of efficient treatments have led to drastic decreases in mortality from cardiovascular diseases, particularly ischaemic heart disease. The decrease in mortality from cardiovascular disease associated with smoking may have resulted in subsequent diagnosis of a lung cancer that would have remained undetected if smokers had died from cardiovascular disease.

Congenital malformation is a risk factor for childhood cancer, for example in the urinary tract. Better survival of children with congenital malformations may have led to greater incidence of several childhood cancers that would otherwise not have occurred.

(3) Changes due to changes in detection methods

The continuous increasing trend in prostate cancer mortality before 1988 was probably due to steadily better identification of elderly patients suffering from prostate cancer (e.g., more systematic blood measurement of alkaline phosphatases and bone X-ray examinations in older patients), that led to increasing certification and registration of prostate cancer as the underlying cause of death (Levi et al., 2004).

Increases in kidney cancer incidence in males and females is mainly attributable to increased incidental detection of these cancers during medical investigations, for instance, abdominal X-ray before surgery, assessment of causes of high blood pressure, or iterative echography of abdominal organs.

For liver cancer, mortality data are not always reliable because the liver is an organ frequently involved in metastatic dissemination of cancers of other organs. As a consequence, many cases of “primary liver cancer” or of death from “liver cancer,” are in fact related to other (sometimes undiagnosed) primary cancers.

The increase in tumours of the central nervous system is most probably due to better disease ascertainment made possible by continuous improvements in non-invasive imaging technologies (e.g., CAT scan, MRI, PET scan). These have permitted the detection of health conditions that in the past remained undiagnosed.

Changes in ultrasound examinations and diagnostic procedures such as fine needle aspiration have contributed to the increase in thyroid cancer incidence (see Section D1).

Diagnosis of pancreatic cancer has been much improved with the advent of new imaging technologies and endoscopic techniques.

Better imaging methods have also played a role in the better identification of causes of death in children, including brain tumours and rarer cancers.

(4) Changes due to early detection and screening

Early detection may follow, and be a result of, the introduction of new detection methods, but is also due to greater disease awareness among patients and doctors, who pay more attention to early symptoms or early clinical signs of cancerous processes. Screening denotes the systematic search for a specific cancer while it is clinically silent.

(4.1) Earlier detection and screening when precursor cancer lesions exist

Cancer mortality can decrease because of higher curability of cancers diagnosed at an earlier stage or because numbers of incident cases are lower. Lower incidence results from the removal of cancer precursor lesions such as polyps in the colon, and intraepithelial neoplasia in the cervix. This scenario appears to apply to colorectal cancer and cervical cancer.

The incidence of and mortality from cervical cancer have steadily decreased because of widespread use of screening modalities able to identify preneoplastic lesions that can be removed. Other factors also play a role, such as lower parity (number of children per mother), gynaecological hygiene and protection against sexually transmitted diseases.

Increasing trends in colorectal cancer incidence contrast with decreasing mortality. Reasons for increases in incidence (e.g., obesity, lack of physical activity) are discussed further below. Until recently, decreasing mortality due to earlier detection and downstaging of cancer was in part driven by greater disease awareness (Autier et al., 2003) and in part by progress in treatment (see below). Implementation of screening for colorectal cancer (e.g., with the faecal occult blood test, FOBT) is likely to further reduce mortality. Also, use of screening methods that can lead to the removal of polyps (i.e., endoscopy and virtual colonoscopy) should reduce both incidence and mortality from this cancer.

(4.2) Earlier detection and screening when precursor cancer lesions do not exist

Early detection and screening that does not involve a cancer precursor lesion and can only aim for earlier detection of cancerous lesions, can still lead to a lowering of cancer mortality because of the greater curability of patients with screen-detected cancer. However, incidence may increase because of increased detection of indolent cancers that would have never (or very slowly) progressed to clinically apparent disease and would probably never have become life-threatening. This scenario appears to apply to breast, prostate and thyroid cancer.

Age-adjusted breast cancer incidence in France has increased by 65% over a 20-year period (the increase in incidence was 82% in women 50 years old or more, and 55% in women below 50 years old), contrasting with a small permanent increase in all-age breast cancer mortality until 1994, after which a decrease of 11.6% occurred between 1995 and 2003 (calculated using joinpoint analysis from US-SEER Programme) (Figures A2.5 and A2.6).

Mammographic screening has played a major role in the increase in incidence of breast cancer, but the rise started well before such screening became available to many women. The increasing trends observed before around 1995 are due partly to greater disease awareness, partly to greater detection by physical breast examination (either self-examination or by a physician or a nurse), partly to changes in reproductive factors, partly to increasing use of hormone treatment (HRT) after menopause, and partly to increasing rates of obesity (see below).

Prostate cancer incidence in France has increased by a factor of 2.6 over 20 years, largely because of the use of testing for prostate-specific antigen (PSA). Mortality from prostate cancer reached its peak in 1988. A slight decline in mortality is observable just after 1988, and between 1989 and 2002, it decreased by 16%. Attribution of this slight mortality decrease to PSA screening is questionable; the peak in mortality of 1988 corresponds to the start of PSA testing and the following upswing of the incidence. It is difficult to assess the contribution of PSA testing that started in 1988 because of the rather long lag-time existing between prostate cancer diagnosis and death. Other factors may have contributed to improving the prognosis of prostate cancer, such as earlier diagnosis (non-PSA-based) and therapeutic progress, including hormonal treatments (see below).

(5) Changes due to changes in exposure to risk or to protective factors

In men, lung cancer incidence and mortality have been decreasing since the late 1980s. In women, incidence and mortality are rising sharply and lung

cancer has almost overtaken colorectal cancer as the second most important cause of cancer death after breast cancer. In men, these trends are mostly attributable to the decreasing number of smokers and also to control of occupational carcinogens. In women, trends are entirely due to the increasing number of French women who smoke.

Cancers of the mouth, pharynx, larynx and oesophagus are strongly related to alcohol consumption and tobacco smoking. A decrease in smoking and alcohol consumption among French males since 1950 (see Sections B1 and B2) was followed by marked decreases in the incidence of and mortality from these cancers. Mortality probably further decreased because of greater disease awareness, leading to earlier diagnosis and more effective treatment.

The increase in primary liver cancer incidence is – at least in part – explained by the increasing number of people in France (and in Europe) infected with hepatitis C virus (HCV). However, the contribution of HCV to liver cancer in France remains to be assessed. Introduction of systematic testing of blood donations for the presence of HCV is likely to curb the epidemic of HCV infection.

Stomach cancer incidence and mortality have dramatically decreased in France and in many other industrialized countries since 1950. The incidence of this cancer continues to decrease but in 2000, it still caused 4940 deaths in France. The decrease in gastric colonization by *Helicobacter pylori* induced by widespread use of antibiotics and more recently, the possibility to detect the presence of that bacterium and to eradicate it, should contribute to further decreases in stomach cancer incidence and mortality. Other possible factors contributing to the temporal changes include food preservation methods (refrigeration instead of salting and smoking) and the availability of fresh fruits and vegetables. However, we still have no firm data confirming the existence or importance of such nutritional factors in relation to stomach cancer burden.

Colorectal cancer incidence is still on the rise, mainly in men, probably because of increases in overweight and obesity and in physical inactivity. Still unidentified dietary risk factors are probably also involved.

Changes in risk factors implicated in the increase in breast cancer incidence include the use of hormone replacement treatment (HRT) and oral contraceptives, changes in reproductive factors, increasing prevalence of overweight and obesity, and decreasing levels of physical activity. The cumulative effects on breast cancer incidence of HRT use and mammographic screening have been described for other countries, such as the USA (California), Sweden, Denmark and Switzerland (Geneva) (see Bouchardy et al., 2006 for a review).

In addition to HRT use, since 1980, a wide variety of progestin-based drugs have been prescribed in France to premenopausal women for treatment of many “female disorders” (e.g., the so-called “luteal insufficiency”, Lowy and Weisz, 2005), and the impact of this practice on breast cancer risk is unknown.

Oral contraceptive use has recently been classified as a Group 1 carcinogen by the IARC (see Section B7), but its use accounts for few breast cancer cases. In contrast, use of oral contraceptives decreases ovarian cancer incidence (see below).

Ovarian cancer incidence and mortality have been decreasing slowly since the late 1980s, probably because of the widespread use of oral contraceptives. It is unknown to what extent the practice of hysterectomy has contributed to these favourable trends in France.

Until the mid-1990s, incidence of and mortality from non-Hodgkin lymphoma (NHL) have doubled over 20 years. Reasons for these increases remain unknown, although current research is focusing on viral and immune factors. Ultraviolet radiation could also be involved, but data are contradictory. The role of chemical pollutants, which were incriminated earlier, has not been supported by more recent data. It should be recalled that the incidence of Hodgkin lymphoma (HL) has markedly decreased and a number of lymphomas previously classified as HL are now classified as NHL. Hence, the incidence of both HL and NHL combined probably deserves more attention than the incidence of NHL alone.

Similarly to most populations of European descent, testis cancer incidence is rising steadily in France for unknown reasons, probably related to changes in lifestyle or in some exogenous risk factor. One current hypothesis focuses on exposure *in utero* to a substance triggering dormant pre-cancerous testicular lesions. After the start of adolescence, under the influence of androgens, these lesions would progress into cancer.

As in other light-skinned populations, incidence of cutaneous melanoma in France has seen a dramatic two-fold increase in the last two decades. Mortality has risen at a lower pace, as most of the increasing incidence concerns early-stage melanomas curable by surgery. Melanoma incidence and mortality in France are still generally on the rise, probably because of delays in the implementation of effective prevention campaigns based on sun protection (Severi et al., 2000).

(6) Changes in mortality due to availability of efficient treatment

Efficient treatment modalities combining chemotherapy, hormone therapy, radiotherapy, surgery and supportive care are now available for most cancers (e.g., Hodgkin lymphoma, leukaemia, breast cancer, colorectal cancer, testicular cancer). These modalities have contributed to the decrease in mortality observed in the last thirty years for a large number of cancers.

Effectiveness of cancer treatments has particularly improved for childhood cancer, resulting in sharp decreases in the mortality due to these cancers in France (Figure A2.9).

(7) Summary of factors likely to be involved in increasing cancer incidence

Table A2.2 summarizes factors known or suspected to be associated with the incidence of common and less common cancers in France. Competing causes, changes in detection and diagnosis and screening effects play important roles in the increase in incidence, whereas it seems that air, water, soil and food pollutants have had little demonstrable impact on cancer occurrence, with the exception of mesothelioma, for which the causal agent (asbestos) is clearly established.

4. Summary graphical representation of temporal trends

Figures A2.10 and A2.11 summarize temporal trends in age-adjusted incidence and age-adjusted mortality of most common cancers (drawings done after Pepin, 2006). The size of the lozenges is related to the incidence rates of cancers in 1997. Notable increases in both incidence and mortality are seen for cutaneous melanoma (in both sexes), liver cancer (in men), NHL (in both sexes), multiple myeloma (in both sexes), lung cancer (in women), kidney cancer (in both sexes), and pancreatic cancer (in both sexes). Increases in incidence and mortality are moderate for lung cancer in men, and for the central nervous system in both sexes.

For breast and prostate cancer, increases in incidence are not paralleled by changes in mortality.

Dramatic decreases in incidence and mortality are observed for stomach cancer (both sexes), cancers of the mouth, pharynx, larynx and oesophagus in men, and cervical cancer in women.

The availability of efficient treatment for testicular and colorectal cancer and leukaemia is manifested in decreases in mortality while incidence was still on the rise in 1997.

As described earlier, mortality data for liver cancer are not always reliable, as many cases of “primary liver cancer” or of death from “liver cancer,” are in fact related to metastasis of other (sometimes undiagnosed) primary cancer.

5. Discussion

This section offers a complementary view to the work done by Remontet and co-workers (2002, 2003), that explored in much more detail cancer incidence and mortality trends in France. The main difference is that this section relies only on data from cancer registries and official mortality statistics and no modelling approach was used to estimate recent mortality or incidence rates at the national level. Interested readers may find detailed statistics on cancer mortality in France on the web-site of the Institut de veille sanitaire (www.invs.sante.fr/cancer_1983_2002/default.htm). The “Atlas de la Mortalité en France” displays in great detail the geographical patterns of mortality from cancer and from other causes (Salem et al., 1999a, b). A comparison between European countries of projections of cancer incidence and mortality data for the year 2006 may be found in Ferlay et al. (2007).

With the ageing of the French population, annual absolute numbers of cancer cases and deaths will continue to increase steadily. The increase in incidence due to ageing is further increased by early detection and screening. Thus, to compare changes in the overall burden of cancer over time that is not due merely to ageing or to screening, the best indicator remains the age-adjusted cancer mortality rate.

Temporal trends in all-cancer mortality in France for men and women resemble those observed in most European countries (Boyle et al., 2003).

Decreasing age-adjusted mortality is due mainly to decreases in the incidence of cancers with high fatality rates, such as lung cancer and cancer of oesophagus in men, of cancer of the cervix uteri in women, and of stomach cancer in both sexes. The decreases in mortality from these cancers in France are attributable mainly to temporal changes in exposure to risk or protective factors, notably smoking and alcohol drinking in men, oral contraceptives in women, and possibly reductions in *H. pylori* infection in both sexes.

Earlier detection has also contributed to decreasing mortality from many cancers, for instance breast cancer, colorectal cancer, cervical cancer, and also cancers for which no systematic screening is organized but diagnosis tends to occur at steadily earlier stage, for instance head and neck cancers.

Most of the increase in cancer incidence is driven by breast and prostate cancer. Increasing breast cancer incidence is induced by changes in reproductive factors, use of HRT and screening. Increasing prostate cancer incidence is largely attributable to PSA screening that detects mainly prostate cancers that are not life-threatening and should not be treated.

Changes in occupational exposures have contributed to the trends in morbidity and mortality due to selected cancers in men, such as mesothelioma and sinonasal cancer. These factors have also contributed to a proportion of lung and bladder cancer, but their influence on trends in incidence of and mortality from these cancers is far less important than that of tobacco smoking.

The available evidence does not allow any temporal trend in cancer occurrence to be attributed with confidence to changes in exposure to pollutants. However, given that levels of exposure to many known carcinogenic agents have drastically decreased during recent decades, one could argue that these agents might have played a role (if any) in cancers with decreasing incidence, rather than in cancers with increasing incidence (e.g., non-Hodgkin lymphomas).

For more frequent cancers such as breast, prostate and colorectal cancers, no or few data exist to support a contribution of occupational factors or pollutants to temporal changes in incidence or mortality.

The decline in cancer mortality observed in France parallels the general decline in cancer mortality in the European Union (EU) in recent decades. Examination of trends in cancer mortality in Europe over the past 30 years has shown that, after long-term increases, age-standardized mortality from most common cancers has fallen since the late 1980s (Quinn et al., 2003).

Progress against cancer in Europe has been the focus of the Europe against Cancer programme of the European Commission that was launched in 1985. It was expected that this programme would foster cancer control efforts in EU Member States and achieve a 15% decline in cancer mortality all over Europe (Boyle et al., 2003). In this respect, the situation in France seems particularly positive, as here, between 1985 and 2002, cancer mortality declined by 21% in men and by 12% in women. It must be noted, however, that for some cancers, the decline in mortality occurred for causes largely independent of coordinated cancer control efforts, for instance, the secular decline in stomach cancer mortality and the secular decline in alcohol consumption in France.

Survival data are often used as an indicator of the severity and of the management of cancers diagnosed in a population. However, survival data do not replace mortality data, as survival may vary considerably over time and between countries for reasons unrelated to treatment or to earlier detection of cancer that would otherwise be diagnosed at a more advanced stage (Boyle and Ferlay, 2005). Survival is considerably influenced by the so-called lead-time bias, that is, the additional time of observation of a cancerous patient due to diagnosis of the cancer at an earlier moment in its progression. Ignoring lead-time gives a biased impression of longer survival that is in fact due to a longer period of observation. Increased detection of more indolent cancers of good prognosis by screening is another source of bias, called length-time bias, that artificially increases survival because proportionally more cancers of good prognosis are included for the calculation of survival duration. One way to control these biases is to take into account stage at diagnosis of cancers registered over time or in different countries. Availability of data on stages often leads to better explanations of cancer survival observed over time or across areas (Sant et al., 2003;

Ciccolallo et al., 2005); this requires registration of stage by cancer registries.

References

Autier P, Boyle P, Buyse M, Bleiberg H. Is FOB screening really the answer for lowering mortality in colorectal cancer? Recent Results in Cancer Research 2003;163:254–263.

Bouchardy C, Morabia A, Verkooijen HM, et al. Remarkable change in age-specific breast cancer incidence in the Swiss canton of Geneva and its possible relation with the use of hormone replacement therapy. BMC Cancer 2006;6:78–85.

Boyle P, d'Onofrio A, Maisonneuve P, et al. Measuring progress against cancer in Europe: has the 15% decline targeted for 2000 come about? Annals Oncol 2003;14:1312–1325.

Boyle P, Ferlay J. Mortality and survival in breast and colorectal cancer. Nat Clin Pract Oncol 2005;2:424-425.

Bray F, McCarron P, Parkin DM. The changing global patterns of female breast cancer incidence and mortality. Breast Cancer Res 2004;6:229–239.

Ciccolallo L, Capocaccia R, Coleman MP, et al. Survival differences between European and US patients with colorectal cancer: role of stage at diagnosis and surgery. Gut 2005;54:268–273.

Doll R, Payne P,Waterhouse JAH., eds (1966). Cancer Incidence in Five Continents, Vol. I. Union Internationale Contre le Cancer, Geneva, Springer.

Doll R, Peto R. The Causes of Cancer. Appendix C, Oxford University Press 1981, pp 1270–1281.

Ferlay J, Autier P, Boniol M, Heanue M, Colombet M, Boyle P. Estimates of the cancer incidence and mortality in Europe in 2006. Ann Oncol 2007;18:581–592.

Hill C, Benhamou E, Doyon F, Flamant R. Evolution de la mortalité par cancer en France de 1950 à 1985. Paris: INSERM 1989.

Hill C, Benhamou E, Doyon F. Trends in cancer mortality. Lancet 1990;336:1262–1263.

Hill C, Benhamou E, Doyon F. Trends in cancer mortality, France 1950–1985. Br J Cancer 1991;63:587–590.

Hill C, Koscielny S, Doyon F, Benhamou E. Evolution de la mortalité par cancer en France 1950–1990, mise à jour 1986–1990. Paris: INSERM 1993.

Hill C, Jan P, Doyon F. Is cancer mortality increasing in France? Br J Cancer 2001;85:1664–1666.

INSERM-CpiDC. www.cepidc.vesinet.inserm.fr, accessed in 2006.

Levi F, Lucchini F, Negri E, Boyle P, La Vecchia C. Cancer mortality in Europe, 1995–1999, and an overview of trends since 1960. Int J Cancer 2004;110:155–169

Lowy I, Weisz G. French hormones: progestins and therapeutic variation in France. Social Sci Med 2005;60:2609–2622

Parkin, D.M., Whelan, S.L., Ferlay, J., and Storm, H. Cancer Incidence in Five Continents, Vol. I to VIII, IARC CancerBase No. 7, Lyon, 2005.

Pepin P. Epidémiologie des cancers en Ile-de-France. Observatoire Régional de Santé d'Ile-de-France, juin 2006. NOT CITED

Quinn MJ, d'Onofrio A, Møller B, et al. Cancer mortality trends in the EU and acceding countries up to 2015. Annals Oncol 2003;14:1148–1152.

Remontet L, Buemi A, Velten M, Jougla E, Estève J. Évolution de l'incidence et de la mortalité par cancer en France de 1978 à 2000. Rapport FRANCIM, Hôpitaux de Lyon, INSERM, InVS, 2002.

Remontet L, Estève J, Bouvier AM, et al. Cancer incidence and mortality in France over the period 1978–2000. Rev Epidémiol Santé Publique. 2003;51:3–30.

Salem G, Rican S, Jougla E. Atlas de la Santé en France. Vol.1 – Les causes de décès. John Libbey Eurotext, Montrouge, 1999.

Salem G, Rican S, Kürzinger ML. Atlas de la Santé en France. Vol.2 – Comportements et maladies. John Libbey Eurotext, Montrouge, 1999.

Sant M, Allemani C, Capocaccia R, et al. Stage at diagnosis is a key explanation of differences in breast cancer survival across Europe. Int J Cancer; 2003;106:416–422.

Segi M. Cancer Mortality for Selected Sites in 24 Countries (1950–1957). Tohoku University of Medicine, 1960.

Severi G, Giles G, Robertson C, Boyle P, Autier P. Trends in mortality from cutaneous melanoma: why are there differences between fair-skinned populations? Br J Cancer 2000;82:1887–1891.

Tubiana M, Hill C. Les progress dans la lutte contre le cancer en France et dans l'Union Européenne. Oncologie 2004; 6:229-244.

WHO Statistical Information System (WHOSIS), Mortality Database. Available from http://www3.who.int/whosis/menu.cfm, accessed March 2006.

Table A2.1 - Numbers of cancer deaths in France in 1968 and 2003 with application of cancer mortality rates observed in 1968 to the French population in 2003 *

	1968						2003							
	Observed deaths		Population figures		Crude rates		Observed deaths		Population figures		Expected deaths †		% change	
Age-group	Males	Females	Males	Females	Males	Females	Males	Females	Males	Females	Males	Females	Males	Females
All ages	58,914	46,865	24,210,936	25,500,088	243.3	183.8	88,201	59,033	28,976,913	30,658,067	94,725	72,765	-6.9%	-18.9%
00-	197	150	2,166,950	2,079,115	9.1	7.2	61	50	1,918,140	1,831,438	174	132	-65.0%	-62.2%
05-	127	109	2,119,613	2,040,697	6.0	5.3	36	37	1,830,796	1,743,294	110	93	-67.2%	-60.3%
10-	130	95	2,095,984	2,021,547	6.2	4.7	52	40	1,943,024	1,852,514	121	87	-56.9%	-54.1%
15-	180	136	2,174,178	2,090,862	8.3	6.5	82	60	1,967,871	1,890,078	163	123	-49.7%	-51.2%
20-	197	116	1,814,075	1,719,705	10.9	6.7	123	76	1,972,712	1,926,700	214	130	-42.6%	-41.5%
25-	216	123	1,475,148	1,387,106	14.6	8.9	149	131	1,915,844	1,899,546	281	168	-46.9%	-22.2%
30-	291	270	1,609,256	1,540,519	18.1	17.5	251	291	2,132,747	2,134,875	386	374	-34.9%	-22.2%
35-	599	570	1,723,373	1,664,195	34.8	34.3	506	641	2,156,834	2,189,424	750	750	-32.5%	-14.5%
40-	1,246	1,142	1,660,855	1,652,799	75.0	69.1	1,286	1,186	2,103,150	2,161,745	1,578	1,494	-18.5%	-20.6%
45-	2,184	1,800	1,388,534	1,423,625	157.3	126.4	3,249	2,135	2,052,795	2,119,910	3,229	2,680	0.6%	-20.3%
50-	2,544	1,862	1,056,750	1,122,283	240.7	165.9	5,918	3,156	2,079,055	2,116,724	5,005	3,512	18.2%	-10.1%
55-	6,044	3,670	1,348,559	1,470,495	448.2	249.6	7,677	3,641	1,676,949	1,706,731	7,516	4,260	2.1%	-14.5%
60-	8,971	4,759	1,219,614	1,403,213	735.6	339.2	7,885	3,739	1,256,452	1,327,729	9,242	4,503	-14.7%	-17.0%
65-	11,076	6,097	998,190	1,284,705	1109.6	474.6	10,743	5,422	1,211,021	1,395,287	13,438	6,622	-20.1%	-18.1%
70-	9,334	7,051	634,909	1,055,863	1470.1	667.8	13,882	7,524	1,095,059	1,408,138	16,099	9,403	-13.8%	-20.0%
75-	7,432	7,468	397,653	775,466	1869.0	963.0	14,599	9,223	844,725	1,251,812	15,788	12,055	-7.5%	-23.5%
80-	5,040	6,273	220,908	486,490	2281.5	1289.4	12,068	9,456	517,013	895,489	11,796	11,547	2.3%	-18.1%
85+	3,106	5,174	106,387	281,403	2919.5	1838.6	9,634	12,225	302,726	806,633	8,838	14,831	9.0%	-17.6%

* Mortality data from the CpiDC, INSERM (2005), Demographic from INSEE

† Expected numbers of deaths calculated from applying cancer age-specific mortality rates in 1968 on numbers of people in each age-group in France in 2003. The numbers of deaths in 2003 divided by the expected numbers of deaths in 2003 (as if rates of 1968 were still valid for 2003), gives the % change in cancer mortality in France between these two periods

Table A2.2 - Factors other than ageing associated with increases in incidence of selected cancer in France

The influence of risk factors displayed in the five columns on the right on cancer incidence and mortality in France is estimated in the remainder of this report.

Keys: (+/–) factor suspected but not confirmed to be involved in a change in incidence; (+) factor moderately associated with a change in incidence; (++) factor involved in change in incidence; (+++) factor strongly associated with change in incidence; (+?) or (++?) association suspected but not proven (?) indicates that there is no evidence for a specific risk factor belonging to the relevant risk factor category

Cancer site	Administrative or demographic reasons	Competing causes	Changes in diagnostic method	Screening effect	Changes in behaviours (a)	Individual risk factors	Reproductive factors	Infectious factors	Air, soil, water, food pollutants
Prostate		+	+	+++					
Thyroid			+++	+++		+/_ (b)			
Breast				+++	+	++ (c, d)	+		
Colorectal				+	++	++ (d)			
Cutaneous melanoma				++	+++				
Lung in women		+			+++				+(i)
Mesothelioma		+			++			?	+++ (e)
CNS tumours			+++						
Hepatocarcinoma		+	+		+			+	
Bladder	+		+						
Multiple myeloma	+		+		+?			++ ?	
Pancreas			+		+			?	
Childhood cancers	+	+ ? (f)	+			?	++ ? (g)	+?	
Testis					?	?	?	?	?
NHL	+		+		?	?		++ ?	?
Kidney			++ (h)		+	+ (d)		?	?

(a) e.g., Tobacco smoking; alcohol; lack of physical exercise; UV exposure; (b) Radiation; (c) Hormone treatment; (d) e.g., obesity; (e) Asbestos; (f) Better survival of children with congenital malformations; (g) e.g., aged mother; prematurity (1.5–2.4 kg), high prematurity (<1.5 kg), and high birthweight (> 4 kg); (h) Mainly incidental detection during medical investigations; (i) Second-hand smoking

Figure A2.1 - Evolution of incidence (1978-1997) and mortality (1950-2004) from cancer in France
Mortality trends in the départements of Bas-Rhin, Calvados, Doubs and Isère are displayed as dotted lines.

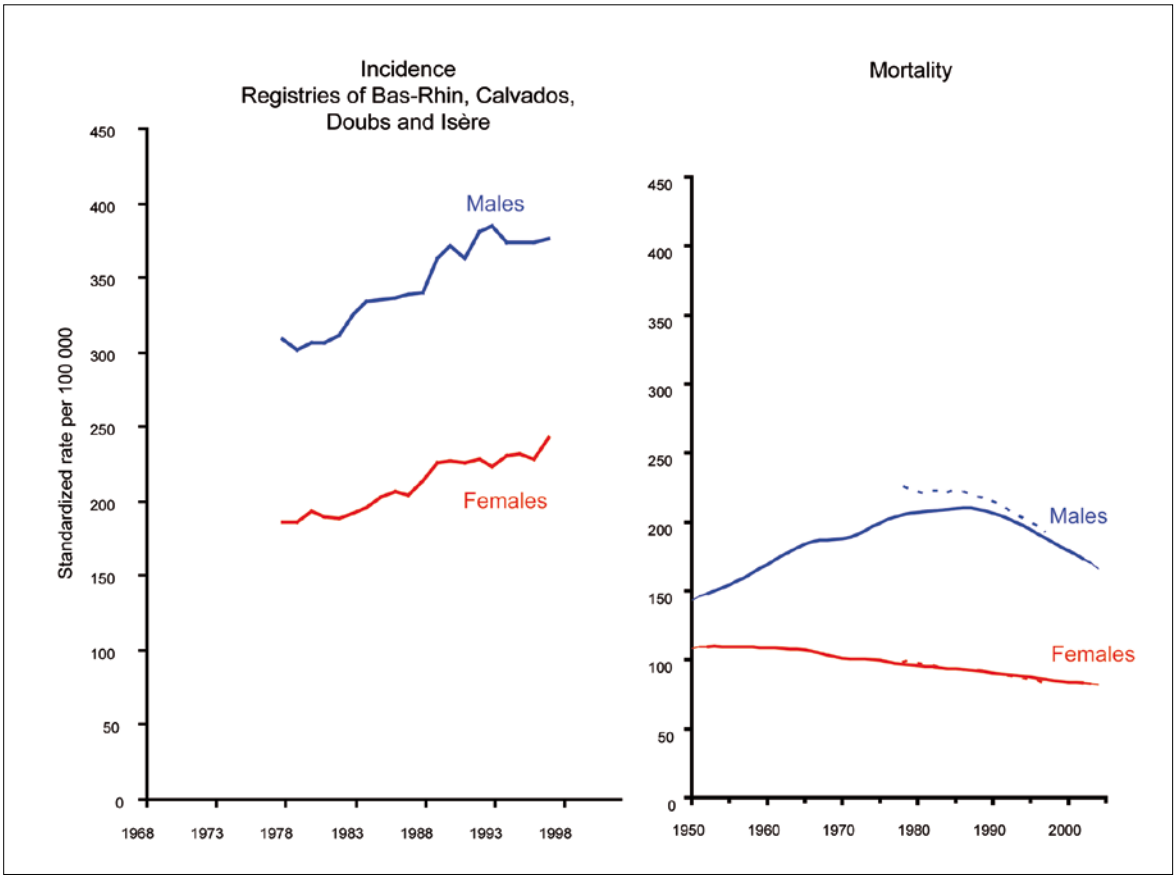


Figure A2.2 - Evolution of incidence (1978-1997) and mortality (1950-2004) by cancer in France
Most frequent cancers - Males

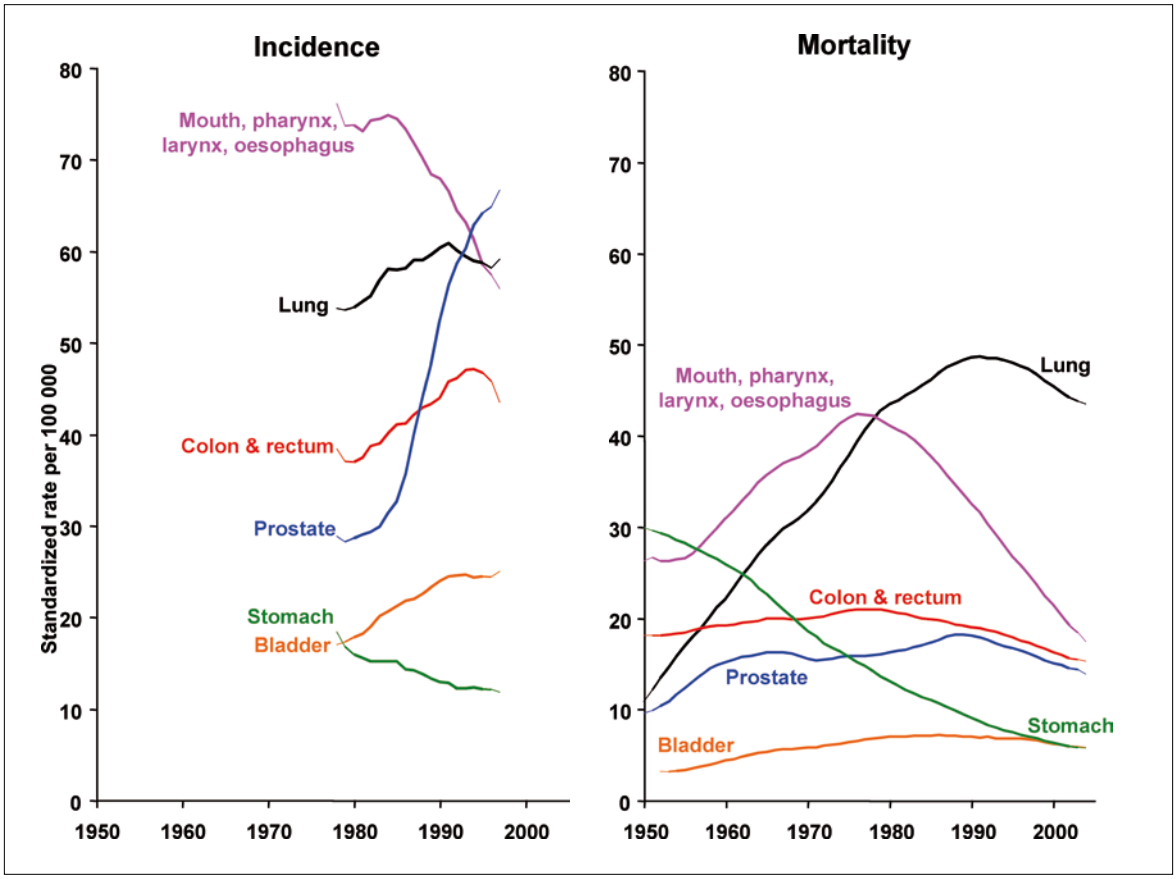


Figure A2.3 – Evolution of incidence (1978-1997) and mortality (1950-2004) by cancer in France
Cancers of intermediate frequency - Males

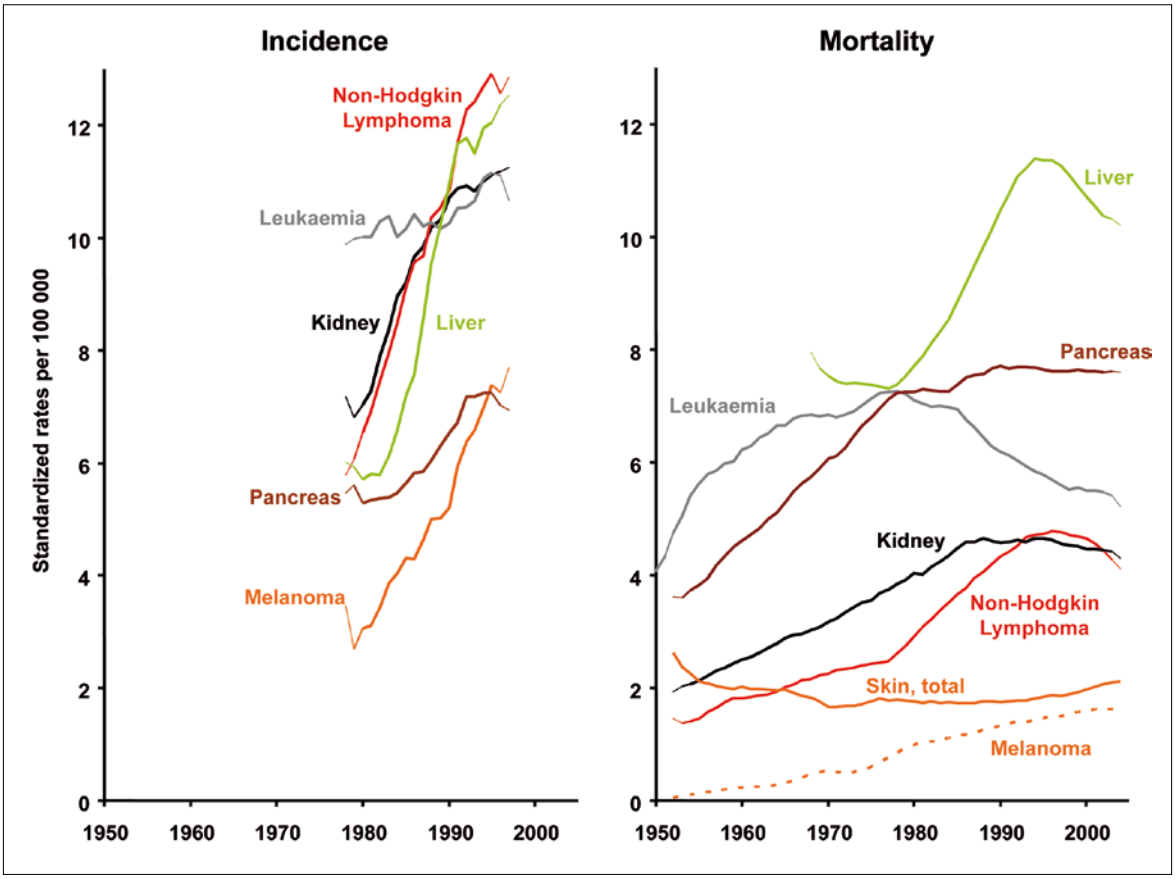


Figure A2.4 – Evolution of incidence (1978-1997) and mortality (1950-2004) by cancer in France
Less frequent cancers - Males

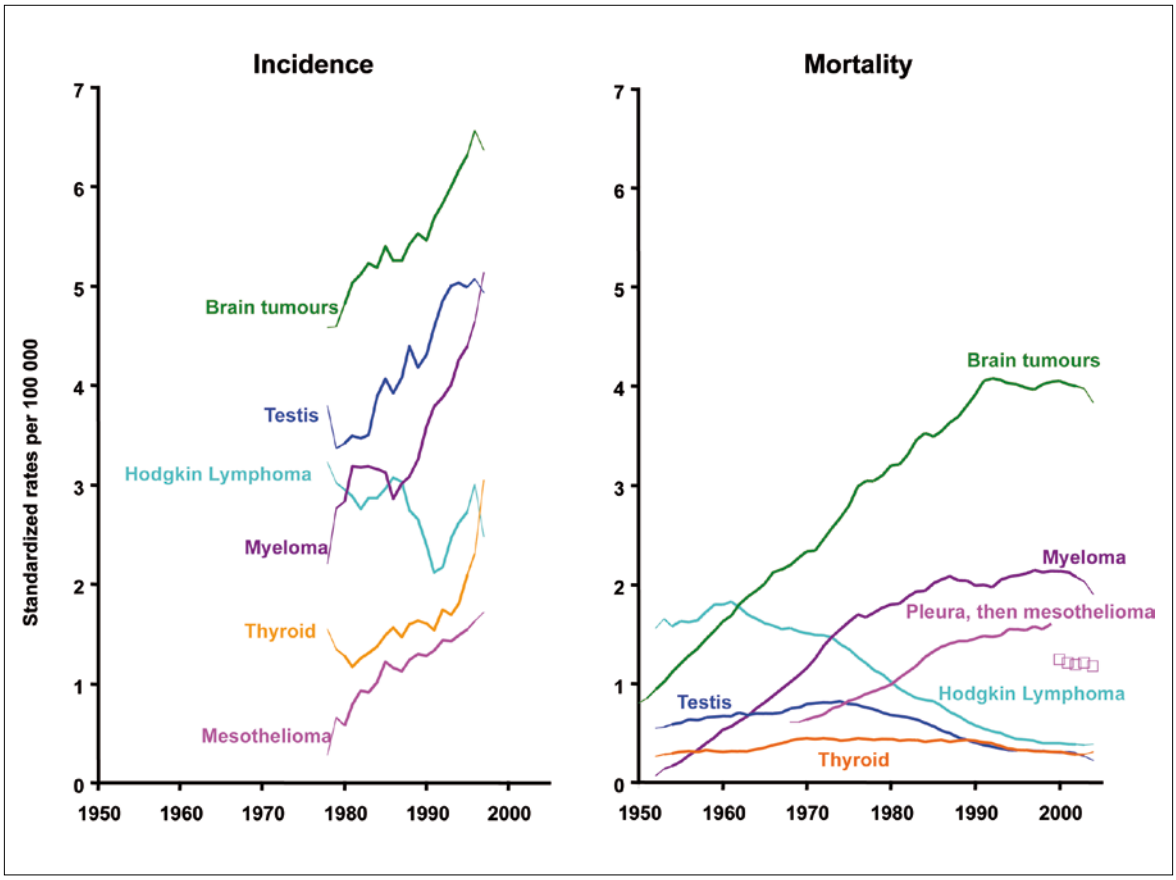


Figure A2.5 - Evolution of incidence (1978-1997) and mortality (1950-2004) by cancer France
Most frequent cancers - Females

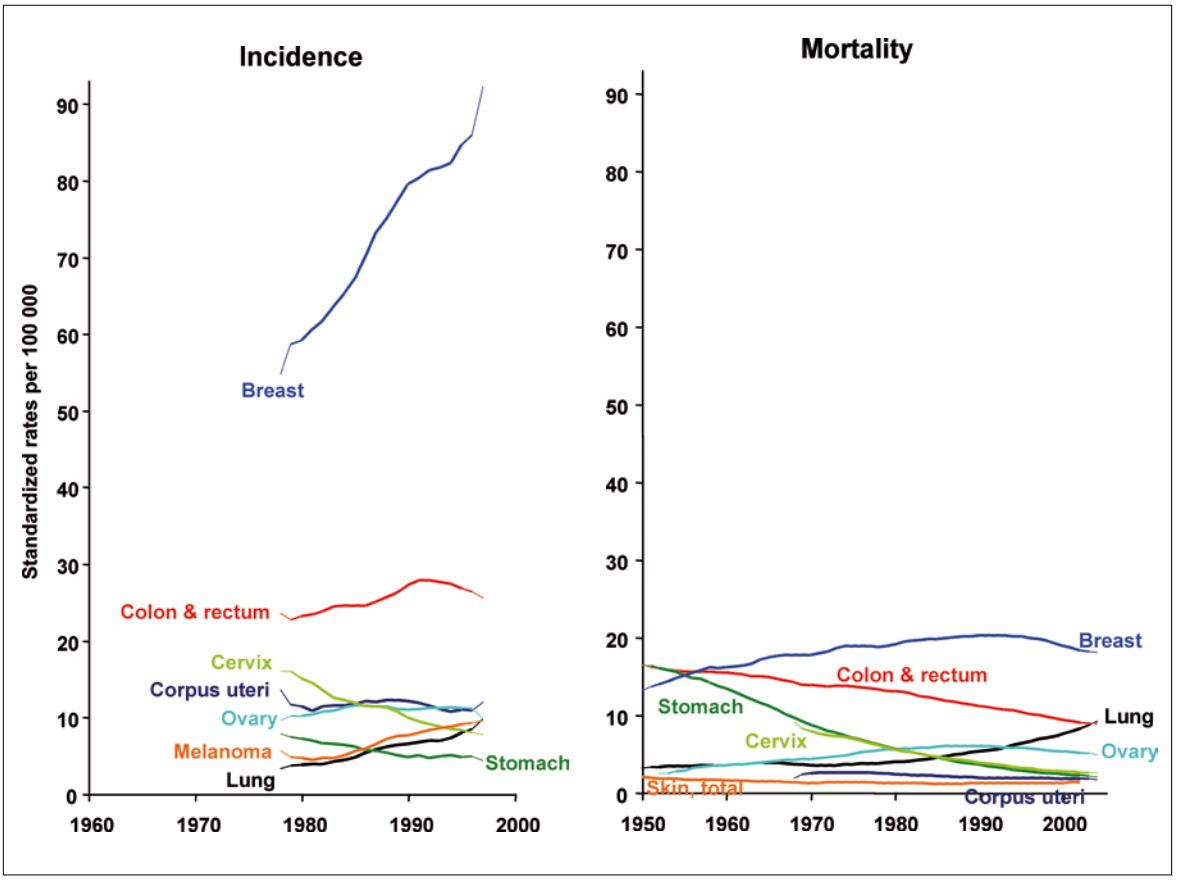


Figure A2.6 - Evolution of incidence (1978-1997) and mortality (1968-2004) of breast cancer in France
Over a 20 year period, breast cancer incidence has increased by 82% in women 50 and older
and by 55% in women younger than 50

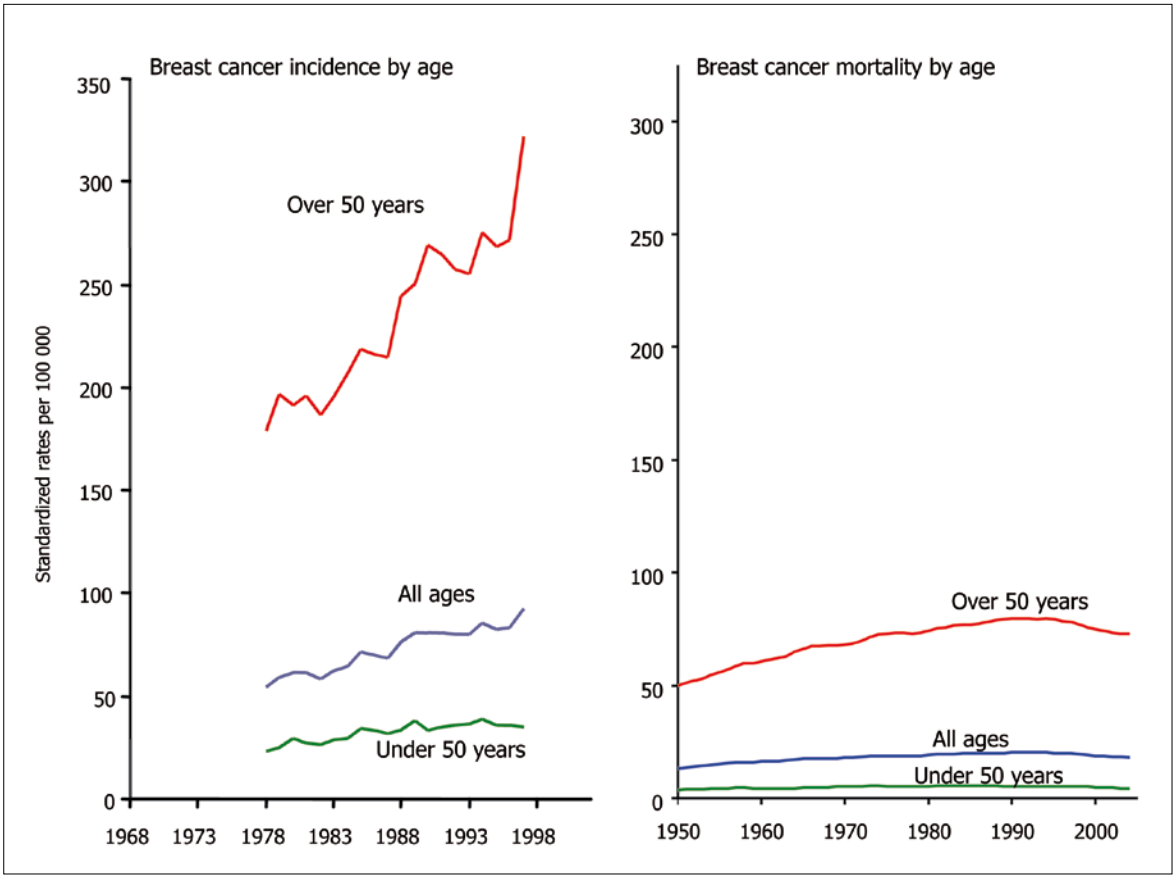


Figure A2.7 – Evolution of incidence (1978-1997) and mortality (1950-2004) by cancer in France
Cancers of intermediate frequency - Females

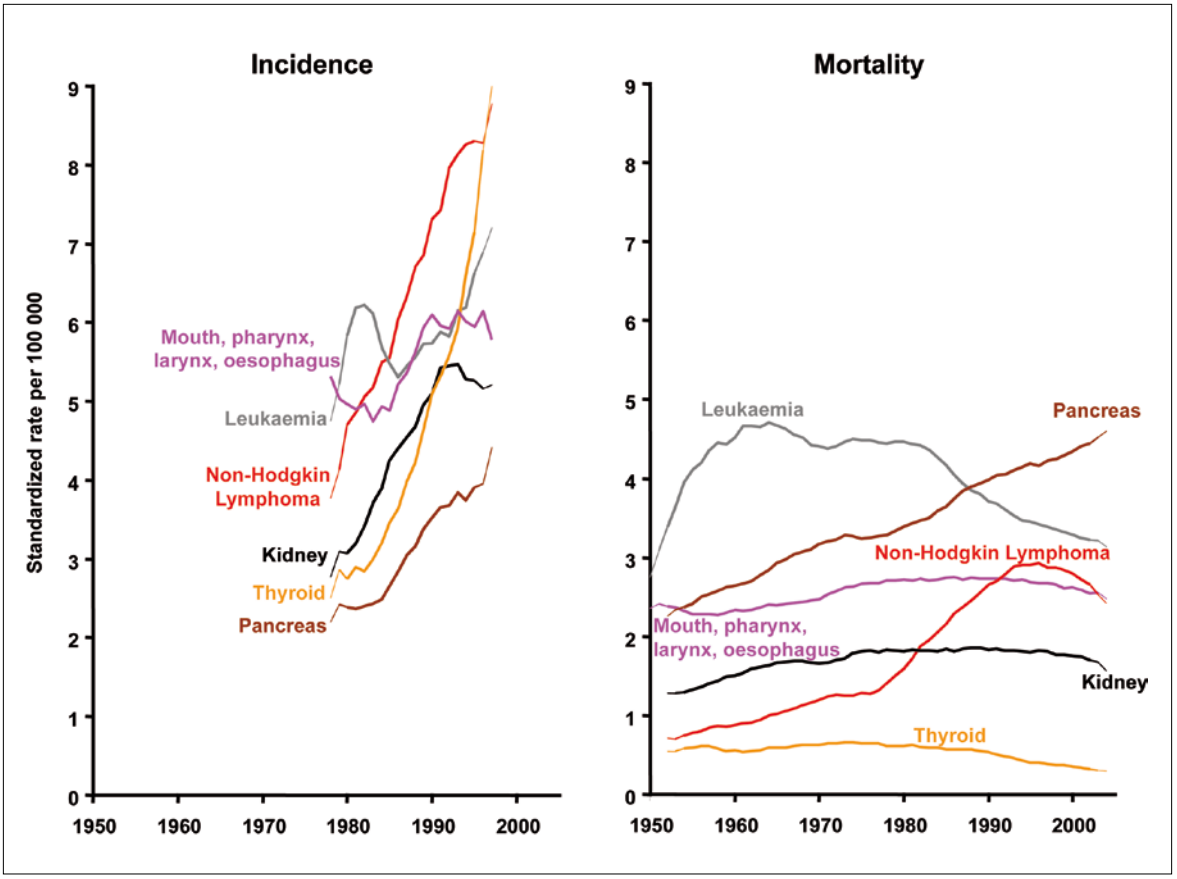


Figure A2.8 – Evolution of incidence (1978-1997) and mortality (1950-2004) by cancer in France
Less frequent cancers - Females

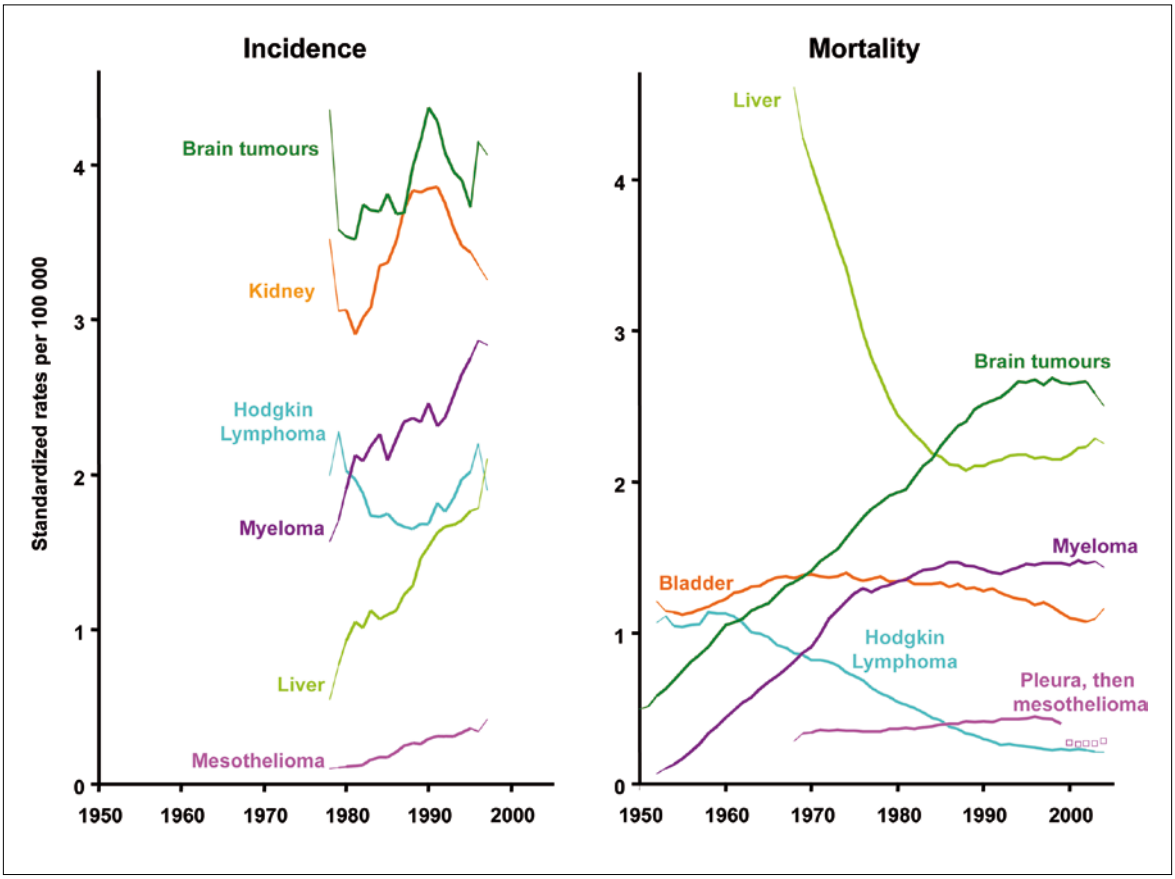


Figure A2.9 – Evolution of mortality (1950-2004) by cancer in France
Cancer in Children (0-14)

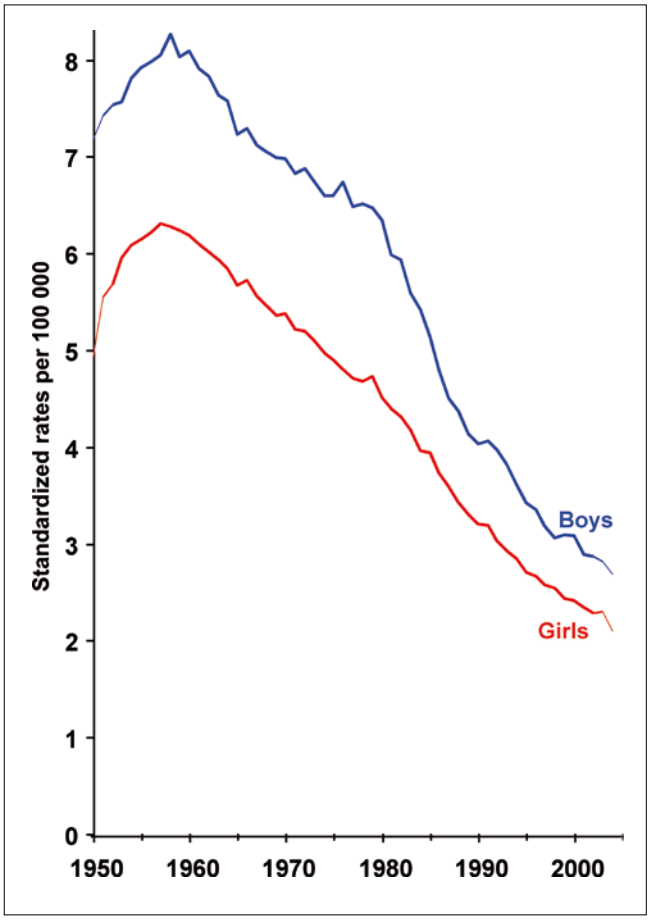


Figure A2.10 - Synthesis of the evolution of the incidence and the mortality from cancer in France, in males, between 1978 and 1997 (rates adjusted by age). The percentages on the ordinate (incidence) and on the abscissa (mortality) indicate the annual average change in the rates of incidence and mortality over the period 1978 to 1997. The size of the points is proportional to the rate of incidence of the cancers

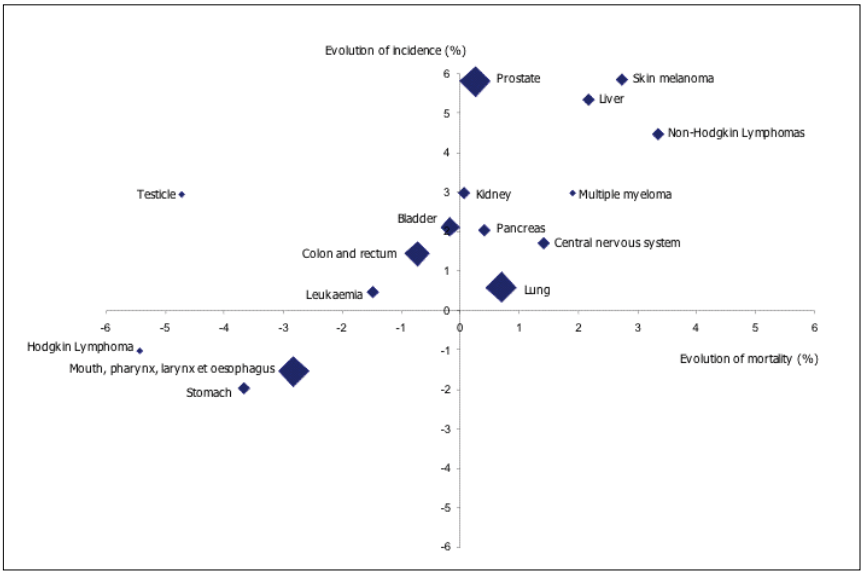
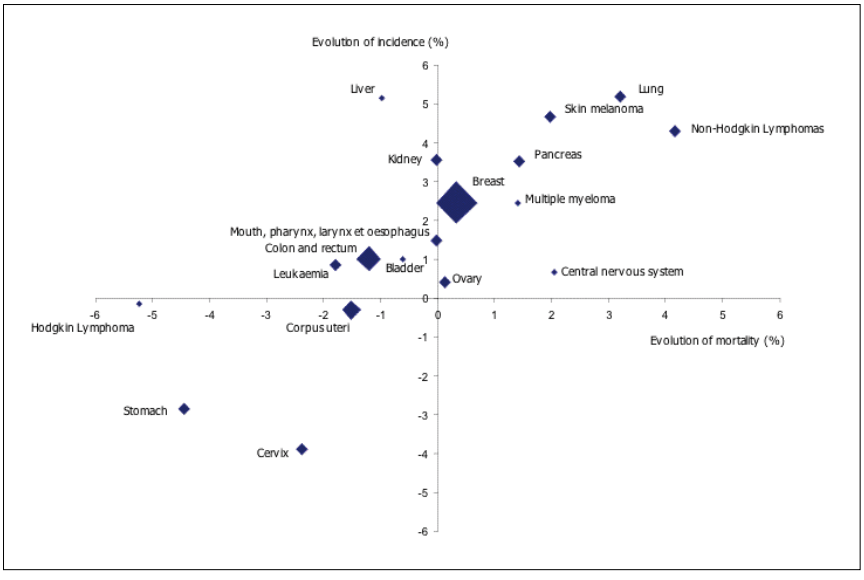


Figure A2.11 - Synthesis of the evolution of the incidence and the mortality from cancer in France, in females, between 1978 and 1997 (rates adjusted by age). The percentages on the ordinate (incidence) and on the abscissa (mortality) indicate the annual average change in the rates of incidence and mortality over the period 1978 to 1997. The size of the points is proportional to the rate of incidence of the cancers



Risk factors selected for estimate calculations

Section B1: Tobacco smoking

1. Definition of exposure

Tobacco smoking causes cancer of the oral cavity, pharynx, oesophagus, stomach, nasal cavity and sinuses, larynx, lung, kidney, urinary bladder, urethra and uterine cervix, as well as acute myeloid leukaemia (IARC, 2004). Because of the length of the latency period, tobacco-related cancers observed today are related to the cigarette smoking patterns over several previous decades. After cessation of smoking, the increase in risk of cancer induced by smoking rapidly ceases: benefit is evident within five years and is progressively more marked with the passage of time. Tobacco smoking also causes many other diseases, most notably chronic obstructive pulmonary disease, ischaemic heart disease and stroke. All forms of tobacco cause cancer. The greatest lung cancer risk is due to cigarette smoking because cigarette smoke is usually inhaled. Cigars and pipes can entail similar risks if their smoke is inhaled. Cigar and pipe smoke are associated with similar risks of cancers of the oral cavity, pharynx, larynx, and oesophagus.

For the purpose of this study, we considered regular smoking of any tobacco product. We considered only smoking status (current and former smoking); duration and amount of smoking were not taken into account. Smokeless tobacco products were not considered because they are not used in France. Exposure to second-hand smoke, an established lung carcinogen (IARC, 2004) is considered among air pollutants (Section B10). The alternative exposure scenario is that of never having smoked.

2. Data used for relative risk (RR) estimates

We conducted a meta-analysis of studies included in the recent IARC Monograph (IARC, 2004). This meta-analysis included all cancers for which a causal association is established, with the exception of sinonasal cancer (small number of attributable cases), nasopharyngeal cancer (small number of attributable cases) and acute myeloid leukaemia (incidence and mortality data not available for France). We calculated sex-specific meta-relative risks for current and former smoking. However, fewer studies were available for tobacco-related cancer in women than in men, and RRs for current smokers among women were sometimes higher than the corresponding RRs for men, but with wider confidence intervals. In view of this statistical instability of RR estimates for women, when RRs in women were higher than in men (or were unknown), the RRs for men were used for both sexes (Table B1.1). Estimates for former smokers among women were also based on few studies, mainly of case–control design. Therefore, instead of estimating RRs for former smokers among women from meta-analyses, we calculated the ratio of the ln(RR) for current smokers to that of former smokers among men and we applied this ratio to the ln(RR) for current smokers among women. We estimated the confidence intervals that were available for this measure using the variance of ln(RR) for current smokers among women (this choice was more conservative than using the variance of the ln(RR) for former smokers among men). For cancer of the cervix uteri, the ratio ln(RR current)/ln(RR former) and the variance used were the average of those of all other sites.

3. Data used for exposure prevalence

Data on prevalence of smoking were abstracted from nationwide surveys (Table B1.2). Prevalence data for 1985 were estimated by linear interpolation using results of surveys conducted in 1983 and 1986, which yielded the following figures for 1985: current male smokers: 48.2%, current female smokers: 30.4%, former male smokers: 27.7%, former female smokers: 14.0%.

4. Calculation of AFs

Table B1.3 lists the AFs and numbers of cancer cases and deaths attributable to tobacco smoking in France in 2000. A total of 43 466 cases of cancer among men (27.0% of the total) and 7095 cases among women (6.1%) were attributable to tobacco smoking. Lung cancer represented about 45% of tobacco-attributable cancers in both men and women; in men, oral cavity and pharyngeal cancer represented an additional 21%. Given the high fatality of many tobacco-associated cancers, corresponding figures for mortality are higher than for incidence (33.4% of all cancer deaths in men and 9.6% in women).

5. Sensitivity analysis

Different lag-times

If a lag-time of 10 years (i.e., using tobacco smoking data for 1990) is considered, prevalence of tobacco smoking for males is lower than in 1985 and prevalence for females is higher. The fraction of incident cancers attributable to tobacco would therefore be 26.8% for men and 6.3% for women. The fraction of cancer deaths attributable to tobacco would be 33.1% for men and 9.9% for women.

If a lag-time of 20 years (i.e., using tobacco smoking data for 1980) is considered, prevalence of tobacco smoking for males is higher than in 1985 and prevalence for females is lower. The fraction of incident cancers attributable to tobacco would therefore be 27.2% for men and 5.5% for women. The fraction of cancer deaths attributable to tobacco would be 33.5% for men and 8.7% for women.

Indirect estimate of the attributable fraction for women

Surveys of tobacco smoking that included only questions on smoking status (current smoker or former smoker) yield prevalence data that cannot be adjusted for the number of cigarettes smoked. Indeed, in surveys conducted in the 1970s, women who declared being current smokers often had very low consumption. Because we used RRs from a meta-analysis that included a large proportion of studies conducted in the USA or in Nordic countries, the pattern of tobacco smoking for women in 1985 described might not have been comparable to that of French women.

We therefore calculated the attributable fraction for tobacco smoking using an indirect comparison for women. Because tobacco smoking is by far the main environmental cause of lung cancer, and because that cancer is not curable, lung cancer mortality statistics are good indicators of the epidemic of cancer associated with tobacco smoking. We hypothesized that in French women, no lung cancer in 1950 was related to tobacco smoking, and any increase in lung cancer mortality rates after 1950 was attributable to tobacco smoking:

AF = (mortality rate in year X – mortality rate in 1950)
/ mortality rate in year X

We performed this calculation for the year 2000 by age group (Table B1.4). These age-specific AFs were applied to age-specific numbers of deaths in 2000, and among the 4246 lung cancer deaths in French women in 2000, 2596 were attributable to tobacco smoking, corresponding to an AF of 61.1%.

6. Comparison with indirect method of calculating AFs

An alternative method of calculating tobacco-attributable risks has been proposed by Peto and colleagues (1992). The method is based on the assumption that current lung cancer mortality provides a better measure of the effect of the exposure of interest – lifetime tobacco smoking – than does smoking prevalence itself. A Smoking Impact Ratio (SIR) is calculated by comparing the lung cancer mortality observed in a given population with that

expected in a (reference) population of non-smokers, typically, rates among never-smokers enrolled in the American Cancer Society Cancer Prevention Study II (ACP-CPS-II). ASIR=1 is equivalent to a population comprising entirely lifetime smokers, and SIR=0 is equivalent to a population comprising entirely never-smokers. An estimate of the number of deaths from cancer and other causes attributable to tobacco smoking in France and other countries in 2000 has recently been calculated (www.deathsfromsmoking.net), based on three groups of cancer: lung, upper aerodigestive tract (oral cavity, pharynx, larynx, oesophagus) and all other cancers. Table B1.5 compares the estimates from that project with those we produced. While figures in men are fairly similar, reflecting the fact that the tobacco epidemic has reached its maturity among French men, discrepancies in women may be partly explained by the fact that the ACP-CPS-II results on lung cancer mortality in non-smoking women in the USA are not applicable to non-smoking French women. The indirect estimate of the attributable fraction for women we calculated above in sub-section 5 suggests that the results of the "deathsfromsmoking" project may underestimate the fraction of lung cancers attributable to tobacco in French women.

7. Discussion

Our analysis confirmed that tobacco is the main avoidable cause of cancer in France among both men and women. There are several reasons why our results for men are likely to represent a conservative estimate of the burden of tobacco-associated cancer. First, we did not include a few rare cancers (cancers of the nasopharynx, nose and paranasal sinuses, myeloid leukaemia) for which a causal association with tobacco smoking has been demonstrated (IARC, 2004). Second, for several other cancers, a causal association with tobacco smoking is suspected, although not yet demonstrated: a notable example is colorectal cancer, for which an association has been reported in several studies. In our meta-analysis, we also calculated summary risk estimates for colorectal cancer: RRs in men were 1.17 for current smoking and 1.16 for former smoking, which would correspond to 2173 incident cases of cancer and 933 cancer deaths. Third, the meta-analysis was based largely on studies conducted in populations smoking primarily or exclusively blond-tobacco cigarettes, while consumption of black-tobacco cigarettes, which is associated with a higher RR of most tobacco-related cancers (IARC, 2004), is a characteristic of French smokers.

On the other hand, as discussed above, the tobacco-related epidemic of lung cancer and other cancers among French women has not yet reached its maturity, while in the UK and the USA, the peak in female smoking was already reached in the 1980s. Also, American and British women used to smoke more than French women (Hill and Laplanche, 2005a). For these reasons, the use of RRs mainly from studies conducted in populations, such as those of the UK and in the USA, in which women have been smoking for a longer time and at higher level might result in an overestimate of the attributable fraction in French women. However, the alternative approach we used to estimate the AF of lung cancer among women (ratio of difference in mortality in 2000 and 1950 over mortality in 2000) suggested that any overestimate was not very large, since it resulted in an AF of 61.1%, comparable to the 69.7% obtained when the method of Levin (1953) was used. Because we cannot exclude the possibility that some lung cancer occurring in 1950 in women was attributable to tobacco smoking, the estimate of 61.1% has to be considered as a minimal AF for French women and the results of the indirect method proposed by Peto et al. (1992) are likely to underestimate the role of tobacco as a carcinogen among French women.

Sensitivity analysis examining a 10- or 20-year lag-time yielded estimates of attributable fractions close to those with a 15-year lag-time.

In our estimates, we did not take into account the average consumption of cigarettes and other tobacco products by French smokers. It is unclear whether the assumption that the level of tobacco consumption is similar in France and in the populations covered by the meta-analysis would result in bias, and if so, what the direction and magnitude of such a bias would be.

In conclusion, the type of tobacco consumed in France and the exclusion of some cancers from our calculations, lead us to consider our estimates of lung cancer cases and deaths caused by tobacco smoking to be minimum values for France in 2000.

Some aspects of the carcinogenicity of tobacco relevant to the burden of cancer in France are dealt with in other sections of this report (Section B10 for

second-hand smoke, and Section C2 for interactions between tobacco smoking and other risk factors).

References

Gandini S, Botteri E, Lodice S, Boniol M, Lowenfelds AB, Maisonneuve P, Boyle P. Tobaccco smoking and cancer: a meta-analysis. Int J Cancer 2007 (in press).

Hill C, Laplanche A. Le tabac en France les vrais chiffres. La documentation Française. Paris, 2004.

Hill C, Laplanche A. Evolution de la consommation de cigarettes en France par sexe, 1900–2003. Bull Epid Hebdomadaire 2005;21–22/2005:94–97.

International Agency for Research on Cancer. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Vol 83, Tobacco Smoke and Involuntary Smoking. Lyon, IARC, 2004.

Levin M. The occurrence of lung cancer in man. Acta Unio Int Contra Cancrum. 1953;9:531–541.

Peto R, Lopez AD, Boreham J, et al. Mortality from tobacco in developed countries: indirect estimation from national vital statistics. Lancet 1992;339:1268–1278.

Table B1.1 – Relative risks (RR) of cancer of specific organs associated with tobacco smoking, by sex*

Cancer site	Men		Women	
	Current smoking	Former smoking	Current smoking	Former smoking §
Oral cavity	4.22	1.57	1.60	1.16
Pharynx	6.82	2.28	3.29	1.67
Oesophagus	2.52	2.13	2.28	1.96
Stomach	1.74	1.34	1.45	1.22
Liver	1.85	1.69	1.49	1.41
Pancreas	1.63	1.10	1.63†	1.10
Larynx	5.24	4.96	5.24†	4.96
Lung	9.87	3.18	7.58	2.78
Kidney	1.59	1.27	1.35	1.17
Urinary bladder	2.8	1.90	2.73	1.87
Cervix uteri	–	–	1.83	1.32‡

* From meta analysis of studies reported in the IARC monograph on tobacco (2004) and Gandini et al. (2007)
§ RRs for former smokers among women were estimated using the ratio of ln(RR current smoker) to ln(RR former smoker) among men that we applied to ln(RR current smoker) for women.
† When RRs for women were higher than for men or when no RR was estimable for women, the RR for men was used instead
‡ For cervix uteri, the ratio ln(RR current)/ln(RR former) and the variance used were the average of those of all other sites

Table B1.2 - Surveys on tobacco smoking in France around 1985 (from Hill and Laplanche, 2005b)

Year	Number		Prevalence (%) of tobacco smoking				Source
			Men		Women		
	Men	Women	Smokers	Ex-smokers	Smokers	Ex-smokers	
1983	941	1036	51		29		CFES§
1983	707	786	55	27	34	18	CFES§
1985 *	–	–	48.24	27.67	30.39	14.00	
1986	960	1040	46		30		CFES§
1986–1987	5874	7280		28		12	INSEE

* Linear interpolation for 1985
§ Comité Français d'Education pour la Santé, now INPES

Table B1.3 – Numbers of cancer cases and deaths attributable to tobacco smoking in France, by sex, for the year 2000

Cancer	Men			Women		
	AF%	Cases	Deaths	AF%	Cases	Deaths
Oral cavity	63.1%	3531	854	17.0%	266	71
Pharynx	76.0%	5619	1943	44.1%	367	138
Oesophagus	51.1%	2065	1777	34.4%	319	239
Stomach	31.1%	1405	981	14.3%	373	288
Liver	37.5%	1882	1884	17.1%	164	273
Pancreas	24.9%	673	904	17.0%	373	546
Larynx	75.9%	2932	1291	64.8%	234	97
Lung	83.0%	19216	17085	69.2%	3178	2939
Kidney	26.4%	1403	499	11.5%	343	127
Urinary bladder	52.8%	4742	1715	39.3%	702	396
Cervix uteri	–	–	–	22.9%	777	336
Total		43466	28934		7095	5449
% of all cancers		27.0%	33.4%		6.1%	9.6%

Table B1.4 – Fractions (AF) of lung cancer attributable to tobacco smoking in French women in 2000, calculated by the indirect method

Age group	Mortality rate in 1950	Mortality rate in 2000	AF (%)
0–29	0.11	0.06	0%
30–39	1.31	1.47	10.9%
40–49	3.65	10.37	64.8%
50–59	8.13	19.48	58.3%
60–69	14.71	29.96	50.9%
70+	16.55	50.22	67.0%
All			61.1%*

*AF for all ages estimated after calculation of AFs for each age category and application of age-specific AFs to the numbers of lung cancer deaths observed in each age category in 2000. See text for more details on the method of calculation

Table B1.5. Comparison of cancer deaths attributable to tobacco smoking in France (2000) in this study and in the "deathfromsmoking" (DFS) project

Cancer	Men				Women			
	This study		DFS		This study		DFS	
	%	No.	%	No.	%	No.	%	No.
Lung	83	17 085	90	18 545	69	2939	42	1774
UADT	65	5866	60	5460	37	545	16	256
Others	10	5984	11	6496	4	1965	1	297
Total	33	28 935	35	30 501	10	5449	4	2327

UADT, upper aerodigestive tract (oral cavity, pharynx, larynx, oesophagus)

Section B2: Alcohol drinking

1. Definition of exposure

The present review focuses on the carcinogenic effects of alcohol drinking and does not take into account other health effects of this habit. Furthermore, no distinction is made according to either type of alcoholic beverage (e.g., beer, wine, hard liquor, home-made spirits) or drinking patterns (e.g., regular versus binge drinking), because the data are inadequate to conclude whether the risk of cancer varies according to these characteristics. The only dimension of drinking which is considered relevant for risk estimate is intake expressed in grams per day of ethanol.

The alternative exposure scenario is that of no alcohol intake.

2. Data used for RR estimates

For all cancers but breast cancer, RRs were extracted from a recent meta-analysis (Corrao et al., 2004). Since all RRs were compatible with a log-linear increase in risk with dose, we fitted a linear regression model to calculate the ln(RR) for intake of an additional gram of ethanol per day. In the case of breast cancer, we used the results of a recent large pooled analysis, which provided an RR of 1.071 for intake of an additional 10 g/d (Hamajima et al., 2002). Table B2.1 lists the RRs used in the analysis.

3. Data used for exposure prevalence

Few temporal surveys on alcohol consumption in France have been reported. We retrieved data from the WHO WHOSIS database (www.who.int) on adult (≥15 years of age) per capita alcohol consumption. WHOSIS alcohol consumption data were calculated from official statistics on production, sales and imports and exports, taking into account stocks whenever possible. We used these survey data as measures of alcoholic beverage drinking because self-reported consumption data are likely to be grossly underestimated. For instance, daily intakes among adults in an INSEE 1986–87 survey could be estimated as 24.7 g in men and 6.0 g in women, considering a standard drink of 10 g; annual total intakes calculated from these figures were well below the WHOSIS data.

Since the consumption figures from economic data were not broken down by sex, we used INSEE survey data to derive the male-to-female ratio in alcohol consumption. In the 1986–87 INSEE survey, consumption was reported as the number of drinks per day; we used a standard amount of 10 g ethanol per drink to estimate the daily consumption (IARC, 1988). In the INSEE survey, consumption was reported by intervals of “number of drinks per day”. Therefore, we took the average of the bounds of each interval for the calculation of daily consumption. The alcohol consumption ratio in the 1986–87 INSEE survey was 4.12; we partitioned the total amount of alcohol drunk per adult in 1985 (derived from the WHOSIS database, 17.22 L of pure alcohol per year) into average daily intakes for men (62.3 g/d) and women (14.4 g/d). This latest partition of alcohol per adult took into account a sex ratio (male/female) of 0.95 to account for slight differences in population size.

4. Calculation of AFs

Table B2.1 lists the results of the calculation of attributable fractions, and Table B2.2 the number of incident cancer cases and cancer deaths attributable to alcohol drinking. A total of 17 398 cases of cancer among men (10.8% of the total) and 5272 cases among women (4.5%) were attributed to alcohol drinking (Table B2.2). Head and neck cancers represented the largest group of alcohol-attributable cancers in men, while breast cancer contributed more than 70% of alcohol-attributable cancers in women. Corresponding figures for mortality are 9.4% of cancer deaths in men and 3.0% in women.

5. Sensitivity analysis

Lag-time

We modified the latency time from 15 to 10 years; the level of alcohol drinking in 1990 was lower than in 1985, with 16.24 litres of pure alcohol consumed per person and per year in France. This represents 58.5 g/d of alcohol for men and 13.8 g/d for women. Using these figures, the fraction of incident cancers attributable to alcohol would be 10.4% for men and 4.3% for women, and the fraction of cancer deaths attributable to alcohol 9.0% for men and 2.9% for women.

We further modified the latency to 20 years. The level of alcohol drinking in 1980 was 19.66 litres of pure alcohol consumed per person. This represents 66.6 g/d of alcohol for men and 20.7 g/d for women. In this case, the fraction of incident cancers attributable to alcohol would be 11.3% for men and 6.3% for women, and the fraction of cancer deaths attributable to alcohol drinking would be 9.9% for men and 4.2% for women.

Standard drink of 12 grams per drink

To estimate the ratio of alcohol consumption between males and females, we relied on the 1986–87 INSEE survey, which reported consumption in drinks per day. We repeated the analysis using 12 g ethanol per drink instead of 10 g. Since the ratio estimate is independent of the dose considered, the resulting male to female alcohol drinking ratio was 4.12. The fraction of incident cancers attributable to alcohol drinking was then similar to the estimate with 10 grams per drink.

6. Discussion

The evidence linking alcohol drinking to cancer risk has been reviewed (Boffetta and Hashibe, 2006; IARC, 2007). There is convincing epidemiological evidence that the consumption of alcoholic beverages increases the risk of cancers of the oral cavity, pharynx, larynx, oesophagus, liver, colorectum and female breast. The risks increase with the amount of ethanol drunk.

Besides increasing cancer risk, alcohol drinking entails complex health consequences, making it difficult to draw conclusions on the net health effect of different drinking patterns. There is some evidence for a J-shaped pattern of risk of total mortality and cardiovascular disease with increasing alcohol consumption. In addition, alcohol drinking increases the risk of injury in all other activities and accident mortality rates are influenced by per capita alcohol consumption. Moreover, alcohol during pregnancy has a detrimental effect on the development of the fetus and its central nervous system, often resulting in malformations, behavioural disorders and cognitive deficits in the postnatal period.

Alcohol drinking in both sexes (Figure B2.2) has considerably decreased in France over recent decades (CNE, 1999) (Figure B2.1), resulting in sharp decreases in alcohol-related diseases such as liver cirrhosis (Figure B2.3) and oesophageal cancer (Figure B2.4).

Although our estimates of the number of cancers attributable to alcohol drinking in men are higher than those derived in the past for the USA or Australia (Holman and English, 1995), they are comparable to those provided for Europe in recent studies (Rehm et al., 2003; Boffetta and Hashibe, 2006). It is noteworthy that alcohol drinking is the second greatest avoidable cause of cancer in French men after tobacco smoking. Sensitivity analysis based on either a 10- or 20-year latency, or using a different standard alcohol content of a drink did not materially affect the attributable fraction estimates.

The accuracy of our estimates is limited by the quality of the available data on individual alcohol consumption. This is particularly problematic because patterns of alcohol drinking in France have undergone major changes during the last 50 years.

References

Boffetta P, Hashibe M. Alcohol and cancer. Lancet Oncol 2006;7:149–156.

Corrao G, Bagnardi V, Zambon A, La Vecchia C. A meta-analysis of alcohol consumption and the risk of 15 diseases. Prev Med 2004;38:613–619.

CNE. Premier Ministre. Commissariat général du Plan. Conseil national de l'Evaluation. La loi relative à la lutte contre le tabagisme et l'alcoolisme. Octobre 1999.

Hamajima N, Hirose K, Tajima K, et al. Alcohol, tobacco and breast cancer – Collaborative reanalysis of individual data from 53 epidemiological studies, including 58,515

women with breast cancer and 95,067 women without the disease. Br J Cancer 2002;87:1234–1245.

Holman CD, English DR. An improved etiologic fraction for alcohol-caused mortality. Austral J Public Health 1995;19:138–141.

International Agency for Research on Cancer. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Vol. 44, Alcohol Drinking. Lyon, IARC, 1988.

International Agency for Research on Cancer. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Vol 96, Alcoholic Beverage Consumption. Lyon, IARC, 2007 (in press).

Launoy G, Milan C, Day NE et al. Oesophageal cancer in France: potential importance of hot alcoholic drinks. Int J Cancer 1997;71:917–923.

OniVins. Enquête sur la consommation du vin en France en 2000: Premiers résultats en matière de fréquences de consommation. Onivins – Infos 2000.

Rehm J, Gmel G, Sempos CT, Trevisan M. Alcohol-related morbidity and mortality. Alcohol Res Health 2003; 27:39–51.

Table B2.1 - Relative risks for alcohol drinking and attributable fractions, by sex

Cancer	Ln (Risk per g/d)	RR for average consumption§		AF%	
		Men	Women	Men	Women
Oral cavity, pharynx	0.020*	3.41	1.33	70.7	24.6
Oesophagus	0.013*	2.23	1.20	55.2	16.9
Colorectal	0.002*	1.13	1.03	11.2	2.7
Liver	0.006*	1.47	1.09	31.8	8.4
Larynx	0.014*	2.34	1.22	57.3	17.8
Breast	0.007†	–	1.10	–	9.4

§ Men: 62.3 g/d ; women: 14.4 g/d

* Based on linear extrapolation from results of meta-analysis (Corrao et al., 2004)

† Based on results of pooled analysis (Hamajima et al., 2002)

Table B2.2 - Number of cancer cases of and deaths attributable to alcohol drinking in France in 2000, by sex

Cancer	Incident cases		Deaths	
	Men	Women	Men	Women
Oral cavity, pharynx	9185	591	2765	180
Oesophagus	2228	157	1918	117
Colorectal	2178	455	936	206
Liver	1593	81	1594	135
Larynx	2214	64	975	27
Breast	–	3925	–	1027
Total	17398	5272	8188	1692
% total cancer cases/deaths	10.8%	4.5%	9.4%	3.0%

Figure B2.1 - Alcohol consumption per adult (age 15 +) per day in grammes in France

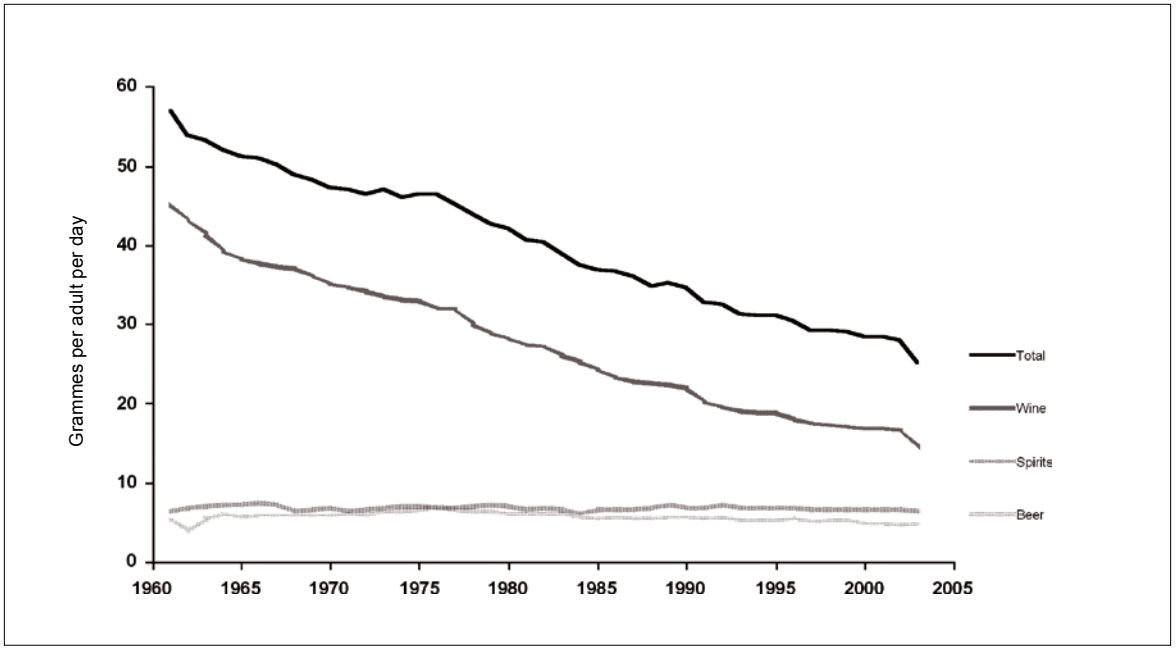


Fig. B2.2 - INRA/ONIVINS surveys on wine consumption in France (ONIVINS 2000)

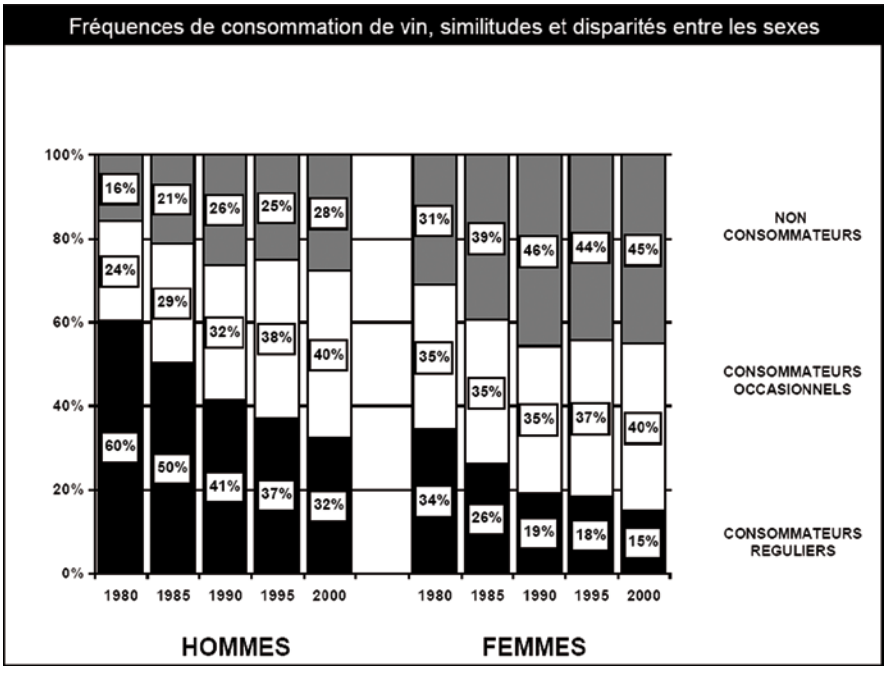


Figure B2.3 Mortality from liver cirrhosis in France
Data sources : INED and WHO Europe (* European standard population was used for rate calculations)

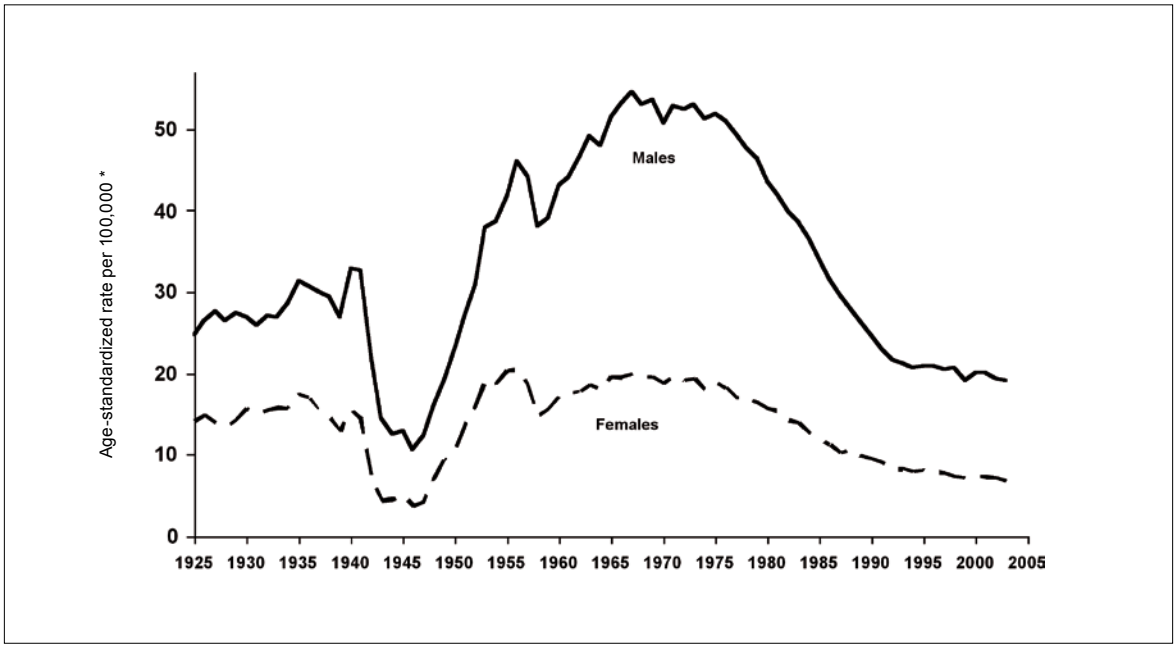
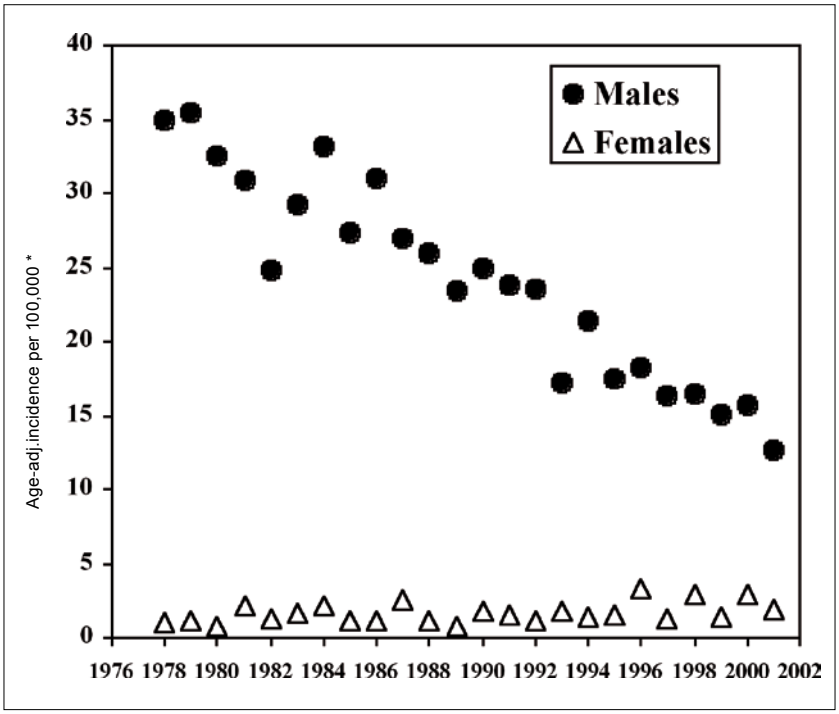


Figure B2.4 - Incidence of oesophagus cancer in Calvados. Incidence per 100 000 person-years, age-adjusted (world population). Data from Launoy et al. (1997), updated by G. Launoy for the needs of this study



Section B3: Infectious agents

1. Definition of exposure

Several infectious agents have been identified as causing human cancer. For most of them, an increased risk of cancer has been demonstrated only in relation to several years of chronic infection. Published epidemiological data in France on some specific cancers or infections were inadequate for estimation of an AF. Table B3.1 summarizes the current list of recognized associations betweens infections and cancer, indicating any reasons for exclusion from this report.

An AF was calculated for cervical cancer and oral/pharyngeal cancer following infection with human papillomavirus (HPV), liver cancer following infection with hepatitis B virus (HBV) and hepatitis C virus (HCV), Hodgkin lymphoma following infection with Epstein–Barr virus (EBV), non-Hodgkin lymphoma following infection with EBV, and stomach cancer following infection with *Helicobacter pylori.*

2. Data used for RR estimates

RRs used in the estimation of AFs are reported in Table B3.2. The RRs of liver cancer following infection with HBV and HCV were derived from a meta-analysis (Donato et al., 1998).

Persistent HPV infection of the cervix is now considered as a necessary and sufficient condition for occurrence of cervical cancer and thus the AF for HPV was considered equal to 1. The RR of oral and pharyngeal cancer following infection with the same agent was derived from a pooled analysis based on Nordic serum banks (Mork et al., 2001).

The RR of stomach cancer following infection with *H. pylori* was derived from a meta-analysis (Eslick et al., 1999).

3. Data used for prevalence

Data on prevalence of exposure to infectious agents are listed in Table B3.2. The sex-specific prevalence of HBV and HCV infection among adults was derived from a recent InVS report (InVS, 2005).

The prevalence of HPV in the anogenital tract was derived from a survey of French women (Clavel et al., 2004); the same figure was used for men. The HPV prevalence in the oral cavity was derived from the pooled analysis of Nordic serum banks (Mork et al., 2001); the same figure was used for men and women.

The prevalence of *H. pylori* infection was derived from a survey of asymptomatic pregnant women (Kalach et al., 2002); this figure was applied to adults of both sexes. One major assumption in the use of such data, in the absence of comparable historical data, is that prevalence of infection has remained stable over time.

4. Calculation of AFs

Although it is well established that EBV is implicated in the occurrence of several cancers, e.g., Burkitt lymphoma (de Thé et al., 1978) and Hodgkin lymphoma (Mueller et al., 1989), there is still great uncertainty as to the extent of these associations (Thorley-Lawson, 2005). For AF estimation, we took figures from the IARC Monograph Vol. 70 on infections and cancer (IARC, 1997), which suggested that 30 to 50% of Hodgkin lymphoma may be due to chronic EBV infection. A similar estimate was also used by Parkin (2006). Non-Hodgkin lymphoma occurring in immunocompromised patients may be due to EBV infection (IARC, 1997), with an estimated AF of 8% (Engels et al., 2005).

Table B3.3 reports the AFs and attributable numbers of cancer cases and deaths for the year 2000. A total of 4206 cases among men (2.6% of the total) and 4871 cases among women (4.2% of the total) were attributable to infections in France in 2000. Liver cancer due to infection with either HBV or HCV represented about half of the infection-related cancer

cases in men, while cervical cancer, all of which is attributed to HPV infection, represented almost 70% of infection-related cancers in women.

Given the high fatality of most infection-related cancers, this group of cancers accounts for a larger proportion of cancer deaths than of cancer cases (Table B3.3).

5. Discussion

The validity of our estimates for France has certain limitations:

(1) The RRs we used were largely derived from other populations (e.g., the effect of different genotypes of hepatitis viruses),

(2) There was a lack of data on prevalence of infectious agents from representative samples of the French population,

(3) There are no historical data on prevalence of infection that would allow us to relate cancers occurring in 2000 to past exposures.

Our estimates are also much lower than those from previous attempts to quantify the burden of cancer attributable to infections (Zur Hausen, 2006; Pisani et al., 1997). Pisani and colleagues (1997) estimated that 9% of cancers occurring in developed countries in 1990 were attributable to chronic infections. More recently, Zur Hausen (2006) estimated that about 20% of human cancer in developed countries could be of infectious origin. This is based on laboratory investigations but also on some epidemiological data. For instance, space–time clustering is often observed for acute leukaemias and NHL (Alexander et al., 1999). Moreover, some risk factors such as agricultural occupations and contact with cattle or meat (butchers, abattoir workers) could be related to a role of viruses. Interestingly, intermittent infections (which “educate” the immune system) and stays in kindergarten appear to have a protective effect. Kinlen (1995) hypothesized that the mixing of two populations with different exposure to a putative viral agent could promote an epidemic of the relevant infection, and some such unidentified infections could be associated with increased leukaemia risk. According to this hypothesis, the high incidence of leukaemia around some nuclear plants would in fact represent a clustering of leukaemia cases due to the arrival of a new population (during and after construction of nuclear plants) who mixed with local inhabitants who had a different history of contact with infectious agents.

The discrepancies between the estimates by these authors and our own may have various explanations:

(1) The prevalence of infectious agents associated with cancer is lower in France than in some other countries; it is certain that a greater proportion of cancers can be attributed to infectious agents in countries where several infectious agents are more prevalent, such as EBV, HIV, HPV or HBV.

(2) Our estimates are based on infectious agents for which (i) there is sufficient evidence for a causal role in the occurrence of several cancers, and (ii) exposure data for France are available. Many other estimates are based on expert opinions, on ecological data or on model approaches, which invariably lead to estimates higher than those based on demonstrated risk levels associated with measured frequency of an agent in a population.

(3) The actual associations between infectious agents and cancer are known to be underestimated, because of the absence of appropriate tools to detect known agents (e.g., detection of HPV in some head and neck cancers). This is the case for agents such as *H. pylori* and EBV that are likely to cause more cancers than those attributable to them solely on the basis of current knowledge of their carcinogenic effects.

(4) Underestimation of AF also results from the absence of proof of a causal role of some infectious agents; for example, some as yet unidentified infectious agents are suspected to play a role in leukaemia and NHL.

Cancers are more frequent in HIV-positive individuals and AIDS patients than in the general population (IARC, 1996b). We could not estimate the burden of cancer associated with HIV carriage and AIDS, as estimates of HIV prevalence in France appear to be incomplete: HIV/AIDS Surveillance in Europe reported 5778 HIV-positive cases in France for 2004, compared with 16 781 in Belgium and 68 556 in the UK (EuroHIV, 2005). It must be mentioned that the introduction of highly active antiretroviral

therapies (HAART) in recent years has led to considerable changes in cancer occurrence among HIV-infected subjects, with a rapid decline in the incidence of AIDS-associated cancers (e.g., Kaposi sarcoma and NHL, but not Hodgkin lymphoma), and an increase of non-AIDS associated cancers (e.g., colon cancer), because of longer survival of HIV-infected subjects and of AIDS patients (Bedimo et al., 2004; Clifford et al., 2005; Del Maso et al., 2005).

It is expected that as coverage with anti-HBV vaccine progresses in France, liver cancer incidence and mortality will start to level off and then decline.

References

Alexander FE; Boyle P, Carli PM, et al. Population density and childhood leukemia: results of the EUROCLUS Study. Eur J Cancer 1999;35:439–444.

Bedimo R, Chen RY, Accortt RA, et al. Trends in AIDS-defining and non-AIDS-defining malignancies among HIV-infected patients: 1989–2002. Clin Infect Dis 2004;39:1380–1384

Clavel C, Cucherousset J, Lorenzato M, et al. Negative human papillomavirus testing in normal smears selects a population at low risk for developing high-grade cervical lesions. Br J Cancer 2004;90:1606–1609.

Clifford GM, Polesel J, Rickenbach M, et al. Cancer risk in the Swiss HIV Cohort Study: Associations with immunodeficiency, smoking, and highly active antiretroviral therapy. J Natl Cancer Inst 2005;97:425–432.

de Thé G, Geser A, Day NE, et al. Epidemiological evidence for causal relationship between Epstein-Barr virus and Burkitt's lymphoma from Ugandan prospective study. Nature 1978;274:756–761.

Del Maso L, Tirelli U, Polesel J, Franceschi S. Trends in cancer incidence among HIV-infected patients. Clin Infect Dis 2005;41:124–125.

Donato F, Boffetta P, Puoti M. A meta-analysis of epidemiological studies on the combined effect of hepatitis B and C virus infections in causing hepatocellular carcinoma. Int J Cancer 1998;75:347–354.

Engels EA, Cerhan JR, Linet MS, et al., Immune-related conditions and immune-modulating medications as risk factors for non-Hodgkin's lymphoma: a case-control study. Am J Epidemiol 2005;162:1153–1161

Eslick GD, Lim LL, Byles JE, et al. Association of Helicobacter pylori infection with gastric carcinoma: a meta-analysis. Am J Gastroenterol 1999;94:2373–2379.

EuroHIV. End-year report 2004 No 71. 2005 (available on www.eurohiv.org).

International Agency for Research on Cancer. Hepatitis B virus. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Vol. 59, Hepatitis Viruses. IARC, Lyon, 1994a, pp. 45–164.

International Agency for Research on Cancer. Hepatitis C virus. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Vol. 59. Hepatitis Viruses. IARC, Lyon, 1994b, pp. 165–221.

International Agency for Research on Cancer. Infection with Helicobacter pylori. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 61. Schistosomes, Liver Flukes and Helicobacter pylori. Lyon, IARC, 1994c, pp. 177–240.

International Agency for Research on Cancer. Human T-cell lymphotropic viruses. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 67, Human Immunodeficiency Viruses and Human T-Cell Lymphotropic Viruses. Lyon, IARC, 1996a, pp. 261–390.

International Agency for Research on Cancer. Human Immunodeficiency Viruses. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 67 Human Immunodeficiency Viruses and Human T-Cell Lymphotropic Viruses Lyon, IARC, 1996b, pp. 31–259.

International Agency for Research on Cancer. Epstein-Barr virus. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 70. Epstein-Barr Virus and Kaposi's Sarcoma Herpesvirus/Human Herpesvirus 8. Lyon, IARC, 1997, pp. 47–374.

International Agency for Research on Cancer. Human Papillomaviruses. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 90. Lyon, IARC, 2006, in press.

InVS. Institut de Veille Sanitaire. Estimation des taux de prévalence des anticorps anti-VHC et des marqueurs du virus de l'hépatite B chez les assurés sociaux du régime général de France métropolitaine, 2003–2004. Janvier 2005.

Kalach N, Desrame J, Bonnet C, et al. Helicobacter pylori seroprevalence in asymptomatic pregnant women in France. Clin Diagn Lab Immunol 2002;9:736–737.

Kinlen LJ. Epidemiological evidence for an infective basis in childhood leukaemia. Br J Cancer 1995;71:1–5.

Mork J, Lie AK, Glattre E et al. Human papillomavirus infection as a risk factor for squamous-cell carcinoma of the head and neck. N Engl J Med 2001;344:1125–1131.

Mueller N, Evans A, Harris NL, et al. Hodgkin's disease and Epstein-Barr virus. Altered antibody pattern before diagnosis. New Engl J Med 1989;320:689–95

Parkin DM. The global health burden of infection-associated cancers in the year 2002. Int J Cancer 2006;118:3030–3044.

Pisani P, Parkin DM, Muñoz N, Ferlay J. Cancer and infection: estimates of the attributable fraction in 1990. Cancer Epidemiol Biomarkers Prev 1997;6:387–400.

Thorley-Lawson DA. EBV the prototypical human tumor virus–just how bad is it? J Allergy Clin Immunol, 2005;116:251–261.

Zur Hausen H. Infections Causing Human Cancer. New York, John Wiley, 2006.

Table B3.1 - Recognized associations of cancer with infections existing in France

Biological agent	Target organ	Reference	Reason for exclusion*
Epstein–Barr virus (EBV)	Hodgkin disease	IARC, 1997	Included
EBV	Non-Hodgkin lymphoma in immunocompromised patients	IARC, 1997	Included
EBV	Nasopharynx	IARC, 1997	P
Human immunodeficiency virus (HIV)	Non-Hodgkin lymphoma	IARC, 1996b	P
HIV	Kaposi sarcoma	IARC, 1996b	P, D
Human papilloma virus (HPV)	Cervix uteri	IARC, 2006	Included
HPV	Oral cavity, pharynx	IARC, 2006	Included
HPV	Anus, penis, vulva, vagina	IARC, 2006	D
Hepatitis B virus (HBV)	Liver	IARC, 1994a	Included
Hepatitis C virus (HCV)	Liver	IARC, 1994b	Included
Helicobacter pylori	Stomach	IARC, 1994c	Included

*D: lack of data on incidence and mortality of the cancers in France

P: lack of relevant data on prevalence or incidence of the infection in France

Table B3.2 - RRs and prevalence of exposure to infectious agents used in the calculation of AFs

Agent	Cancer	RR	Prevalence of infection %	
			Men	Women
HBV	Liver cancer	18.8	1.19	0.16
HCV	Liver cancer	31.2	0.73	0.99
HPV	Cervical cancer	∞	15.3*	15.3*
HPV	Oral pharyngeal cancer	2.1	6.5	6.5
H. pylori	Stomach cancer	2.04	21.3	21.3

*Not used for AF calculation, that is assumed to be 100%

Table B3.3 – Numbers of cancer cases and deaths attributable to chronic infection in France, by sex, for the year 2000

Cancer	Agent	Men			Women		
		AF%	Cases	Deaths	AF%	Cases	Deaths
Hodgkin lymphoma	EBV	40.0%	294	67	40.0%	252	47
NHL	EBV	8.0%	442	182	8.0%	350	175
Liver	HCV	18.1%	906	907	23.0%	221	368
Liver	HBV	17.5%	876	877	2.8%	27	44
Stomach	*H. pylori*	18.1%	820	572	18.1%	473	365
Oral cavity and pharynx	HPV	6.7%	867	261	6.7%	160	49
Cervix uteri	HPV	–			100%	3387	1463
Total			4207	2866		4870	2511
% all cancers			2.6%	3.3%		4.2%	4.4%

Section B4: Occupation

1. Definition of exposure

In this study, we took into account occupational exposures for which a causal association with human cancer has been definitely established (Siemiatycki et al., 2004). A number of established occupational carcinogens, however, have not been used in recent decades (e.g., mustard gas, chloro-methyl ethers) and are not further considered. In the case of vinyl chloride and formaldehyde (Cogliano et al., 2004), the tumours causally associated with the exposure are very rare (angiosarcoma of the liver and nasopharyngeal carcinoma, respectively) and estimates of attributable cases of cancer are not given because these figures are very low. We did not calculate an AF for occupational exposures to X-rays for reasons discussed in Section D1.

In addition to specific agents and groups of agents, IARC has classified several exposure circumstances (mainly industries and occupations) as Group 1 carcinogens. With the exception of painting, the rubber industry and boot and shoe manufacturing, these were not included in the estimates of AF because either the relevant agents were already included in the estimate (e.g., cabinet and furniture making represented by the agent wood dust) or they are industries or occupations that have no longer been operating in recent decades (e.g., coal gasification).

For all occupational agents, the alternative exposure scenario is that of no exposure.

2. Data used for RR estimates

RRs were extracted from recently published meta-analyses or pooled analyses. If no such meta-analysis was available, one was performed *ad hoc* for this project on the basis of original published articles and recent reviews. B4.1 lists the RRs, most of which were derived from meta-analyses performed at the IARC[1]. Practically all RRs were derived from studies in men; RRs were assumed to be equal in women.

For occupational exposure to radon, we used a specific approach outlined below.

3. Data used for exposure prevalence

The prevalence of exposure to the agents included in the analysis is shown in Table B4.2.

For most agents, the number of exposed workers was obtained from the SUMER 1994 survey, that provided estimates of the numbers of workers employed in each industry (SUMER 1994). The SUMER 1994 survey was conducted in 1994 by 1205 occupational physicians, who each recorded the exposures experienced by 50 workers randomly selected in their practices. The survey included samples from approximately 7 000 000 male and 5 000 000 female workers, mostly employed in the private sector. It notably excluded farmers, civil servants and self-employed workers. We adopted the following steps to estimate the prevalence of lifetime occupational exposure for the French population older than 15 years old in 1994 (22.3 million men and 24.2 million women in 1994, according to INSEE):

Step 1: Active population from SUMER 1994: We estimated the prevalence of occupational exposures in the SUMER 1994 population, representing 7 000 000 active males and 5 000 000 active females. Because this was a study among the active population, we took the population to be aged 15–64 years.

Step 2: Active population not covered by SUMER 1994: The INSEE statistics show that the overall active population 15–64 years old in France in 1994

[1] The meta-analytical work was done for this project, and involved review of large series of studies. User-friendly summary tables of this work are now under construction, and are available upon request.

comprised 14 million males and 11 million females. We thus calculated that the active population 15–64 years old not covered by SUMER 1994 represented 7 million males and 6 million females. We applied to this population half of the occupational exposure prevalence estimated from SUMER 1994 in Step 1.

Step 3: Inactive population: The INSEE statistics for 1994 indicate the presence of 4.9 million inactive men and 7.6 million inactive women aged between 15–64 years old. Because this population could have been exposed during an occupation prior to an unemployment period, we considered that inactive people 15–64 years old had an occupational exposure prevalence equal to one fourth of the prevalence estimated from SUMER 1994 (Step 1).

Step 4: Population over 65 years old: The INSEE statistics show that there were 3.4 million men and 5.6 million women aged 65 years old or more in 1994. For this population, we applied a prevalence of past exposure corresponding to the prevalence computed for the overall age group 15–64 years old (Steps 1–3). To account for the fact that in this population the rate of unemployment was lower, and to account for the secular decrease in exposure to occupational carcinogens, we applied a correction factor of 1.25 to the prevalence of occupational exposure derived from the SUMER 1994 survey for the 15–64 year age group.

Step 5: Correction factor for lifetime exposure: Finally, we had to take into account the fact that the SUMER 1994 survey was a cross-sectional study (i.e., done at a precise moment) and concerned only the last job held. Hence, for estimation of lifetime occupational exposure prevalence, a factor of 3 was applied, based on the ratio between cross-sectional (last job) and lifetime prevalence of exposure to respiratory carcinogens estimated among controls included in a European multicentric case–control study of laryngeal cancer and occupation (Berrino et al., 2003). This ratio of 3 represented an average number of positions held during professional life.

Exposure to polycyclic aromatic hydrocarbons was estimated by adding together the SUMER exposures to polycyclic aromatic hydrocarbons, to combustion fumes and to tar and pitch. In the case of exposure to mineral oils, the SUMER survey did not distinguish between untreated and mildly treated oils, and treated oils. A greater role in cancer is established for untreated and mildly treated oils. A separate survey estimated that 37% of French workers exposed to mineral oils in various industries were exposed to untreated and mildly treated oils (INRS, 2002), and we applied this proportion to the total number of mineral-oil exposed workers in SUMER. Exposure to inorganic acids in the SUMER survey was not taken into account because the carcinogenic agent 'strong inorganic acid mists containing sulfuric acid' represents only a small fraction of it.

The SUMER 1994 survey did not include estimates for radon exposure, and we adopted a specific approach for this agent (see below). In the case of asbestos, the AF was estimated in a different way than for the agents listed above (see sub-section B4.4).

Occupational exposure to wood dust represents a special case in France because of the high proportion of workers exposed to hard wood dust, which entails a higher risk of sinonasal cancer compared with soft wood dust; most studies have been conducted among workers exposed to soft wood dust (Demers et al., 1995). The calculation of AF based on the SUMER exposure data and the results of occupational cohort studies (Demers et al., 1995) yielded a figure that was lower than the number of cases of sinonasal cancer receiving compensation for occupational exposure to wood dust (87 men in 2000) in France (Direction des Relations du Travail, 2002). We therefore used the number of compensated cases in men for calculation of the AF of sinonasal cancers attributable to wood dust, and applied the same AF to cancer deaths. It is worth noting that numbers of sinonasal cancers due to wood dust exposure may be underestimated because only salaried workers receive compensation, but not craftsmen (e.g., cabinet makers) because they are independent workers. However, the real numbers are not known. No compensation for sinonasal cancer in women was reported by the Direction des Relations du Travail (2002), but professional exposure of women to wood dust is rare.

The prevalence of having ever had employment as a painter or in the rubber industry was derived from controls included in the European multicentric study of laryngeal cancer and occupation (Berrino et al., 2003).

4. Calculation of the AF for asbestos

Asbestos is a natural silicate fibre that causes lung cancer and mesothelioma of the pleura and peritoneum. It is a major occupational carcinogen. In France, in 1906, the first report was issued on high mortality rates observed in a textile factory using asbestos in Condé-sur-Noireau, Calvados (Sénat, 2005). Massive imports of asbestos in France started after 1945, peaked in the 1970s and 1980s and considerably decreased since 1990; use in industry and building construction was forbidden on 1 January 1997 (Sénat, 2005). To estimate the AF of mesothelioma for asbestos, we used the results of the French National Mesothelioma Surveillance Programme: 83.2% (95% CI 76.8–89.6) for men and 38.4% (95% CI 26.8–50.0) for women (Goldberg et al., 2006).

For lung cancer, we used the RR reported in a meta-analysis of 69 occupational cohort studies (Goodman et al., 1999). Data on prevalence reported in the SUMER 1994 survey probably grossly underestimate lifetime exposure prevalence, given the sharp decline in prevalence and level of asbestos exposure experienced in all European countries since the early 1980s. We therefore used data on prevalence reported in a multicentric French case–control study (Iwatsubo et al., 1998). In this study, medium to very high probability of exposure to asbestos represented 9.1% of all job periods. We used this figure as the prevalence of occupational exposure in men. No reliable data exist for women. We estimated the ratio of number of cases of lung cancer to mesothelioma attributed to asbestos among men (ratio = 1.7) and applied it to the number of mesotheliomas attributed to asbestos for women.

5. Occupational exposure to external ionizing radiation

According to French law since 1966–1967, workers occupationally exposed to radiation above natural background levels have had to wear individual dosimeters. In 1985, the Service Central de Protection contre les Rayonnements Ionisants (SCPRI) was responsible for collecting the recorded doses, but several private and public laboratories, using specific derogations, were allowed to make their own measurements. Their data were then collected by SCPRI and added to the individual dose files, but no annual synthesis was made before SCPRI was transformed into the Office de Protection contre les Rayonnements Ionisants (OPRI), which produced its first annual report in 1995.

From 1995 to 2005, the number of workers occupationally exposed to external ionizing radiation has shown little variation. Such exposure concerns about 140 000 medical and veterinary workers, 60 000 nuclear industry workers, 25 000 to 40 000 non-nuclear industry workers and 20 000 other workers including research and control staff (Ministère du Travail, 2006). We have assumed that the same figures applied ten years earlier.

The first overall values reported by OPRI in 1995 covered 246 945 workers, of whom 187 000 were directly followed by OPRI. The risk descriptor recommended for radiological protection purposes is the sum of the individual doses, called “collective dose”; in the group followed by OPRI in 1995 this amounted to 84 man Sv (the so-called man.sievert unit). Only 10% of individual doses were greater than zero and 46 individual doses were higher than the legal limit, which at that time was 50 mSv/year. This limit did not change between 1985 and 1995, but improvements in radiological protection, following the ALARA (as low as reasonably achievable) principle, led to a continuous decrease in both individual and collective doses. Considering doses above 10 mSv in the same OPRI group, 250 (out of a total of more than 600 for the whole group) were recorded in 1995, 350 in 1985 and 700 in 1975. This provides a weighting factor which suggests that the collective dose in 1985 was about 185 man Sv for the whole group of exposed workers. Since then, collective doses have continuously decreased from about 120 man Sv in 1995, to 90 man Sv in 2000 and 65 man Sv in 2005. In 2005, about 95% of the workers who had dosimetric monitoring received annual doses below 1 mSv; 5% in the range 1 to 20 mSv, and less than 0.02% above 20 mSv.

In the year 2000, on the basis of a nominal risk of 4% of fatal cancer per Sv among workers, linear extrapolation would imply an engaged risk of less than 10 cases for the 185 man Sv recorded in 1985. However, the International Commission on Radiological Protection (ICRP) does not recommend the use of the collective dose to calculate cancer risk estimates (this calculation would support the validity of

the linear relationship with no threshold for assessing low-dose risk). Estimation of an attributable risk for such occupational exposures should therefore rely on individual exposure history, and on risk estimates for different dose ranges, assuming no a priori dose–risk model and taking into account accurate estimates of the main potential confounding factors, such as tobacco or alcohol consumption, but such data are not available.

As a result of the inclusion of leukaemia, bone sarcoma and lung cancer in the official list of occupational diseases associated with exposure to ionizing radiation, 20 to 30 cases of cancer per year in France have been legally acknowledged as related to occupational exposure to ionizing radiation, but this administrative process does not have scientific value.

6. Occupational exposure to radon

Uranium mining started in France in 1946 and ended in 2001. Exposure levels and cancer mortality in the cohort of 5098 French miners were extensively recorded by Cogema and the Institut de Radioprotection et de Sûreté nucléaire (IRSN) from 1983 up to December 1999. Individual cumulative exposure resulted in an average effective dose equal to 185 mSv. No cancer excess was observed for exposure levels below 150 Bq/m3 (Rogel et al., 2002). Excess relative risk for cancer at higher exposures was found at 0.16% per effective mSv. In 1994, lung cancer was the cause of death in 126 out of 1162 deceased miners and in 1999 it accounted for 159 out of 1471 deceased miners (IRSN “Le radon”.www.irsn.org/document). Correcting for expected deaths from lung cancer in non-exposed people would imply that about three deaths were attributable to occupational radon exposure in the year 2000 in this cohort.

Occupational, above-ground exposure to radon is not documented in France, although according to regulatory policy implementing European directive 96/29 since 2003, the responsible operators are asked to monitor exposure and reduce levels above 400 Bq/m3. However, the regions of the country and the workplaces which may be of concern have not yet been identified by a specific regulation and so far results of the survey are very scanty. One can make only very crude estimates of the prevalence of exposure and therefore of the number of attributable lung cancers. Conversion of exposure levels in Bq/m3 in terms of mSv is also a matter of debate. ICRP 65 suggests a conversion of about 7 mSv for a 2000 hours of exposure to 1000 Bq/m3, which represents the level of action for the International Atomic Energy Agency (IAEA - Basic Safety Standards No. 115). This is directly derived from conversion factors obtained from miners, but it may be supposed that in France, during work in exposed areas, breathing patterns and equilibrium factors are more comparable to indoor exposure, which would result in a lower conversion factor of about 5 mSv per 1000 Bq/m3 at work.

The United Nations Scientific Commitee on the Effects of Atomic Radiation (UNSCEAR 2000) provided a crude estimate of occupational exposure above the ground on the basis of enquiries in the United Kingdom and Germany. It was estimated that about 50 000 workers in the United Kingdom were exposed to an average dose of 5 mSv per year, resulting in a collective dose of about 250 man-Sv; in Germany 70 000 workers were estimated to be exposed to 1000–3000 Bq/m3. UNSCEAR proposed to adjust the expected worldwide occupational, collective dose resulting from radon above the ground on the basis of gross domestic product (GDP). This would lead to very similar numbers in France and the United Kingdom, accounting for about 10 fatal cancers in the year 2000.

Another way to deal with this problem is to consider that exposure levels at work are similar to indoor exposure levels. According to IRSN (Robé and Tirmarche, 2003), 7% of the collective dose to radon indoors is due to exposure levels above 1000 Bq/m3. Assuming there were 22 million workers in 1985, the collective dose to radon would be about 30 000 man Sv, with some 7% of workers exposed to 1000 Bq or more, resulting in 2100 man Sv for 7000 hours indoors; for 1600 hours of work time in 1985, this leads to a collective dose of about 500 man.Sv per year.

There is little doubt that levels of exposure in the range of 1000 Bq/m3 or more are associated with lung cancer. With a nominal coefficient of 4% of lung cancer deaths engaged per Sv, this will result in 20 deaths attributable to occupational above-ground radon in the year 2000 assuming that the annual collective dose was constant. Including the French miners cohort leads to an estimate of 23 deaths attributable to radon.

7. Calculation of AFs for other agents

Table B4.3 lists the calculated AFs for incident cancer cases and deaths. For the year 2000, a total of 4012 cases of cancer among men (2.5% of the total) and 316 cases among women (0.3%) were attributed to occupation. Asbestos, polycyclic aromatic hydrocarbons (PAHs) and chromium VI were the main occupational carcinogens. Because of the high fatality of most occupation-related cancers, the number of cancer deaths is close to that of incident cases, but the percentages over total cancer deaths are higher (3.7% in men and 0.5% in women). Table B4.4 summarizes mortality results by type of cancer. The results in Table B4.4 do not take into account potential interactions between exposures. These are addressed in detail in Section C2.

In the case of untreated and mildly treated mineral oils, which are causally linked to squamous-cell carcinoma (SCC) of the skin, we calculated an AF only for mortality (assuming that nearly all deaths from non-melanoma skin cancer are due to SCC), since no reliable data exist on incidence of non-melanoma skin cancers.

8. Discussion

There are several reasons why we may have underestimated the burden of occupational cancer. These include the lack of consideration of suspected occupational carcinogens such as diesel engine exhaust and some groups of solvents; the non-inclusion of some established carcinogens because reliable exposure data were not available (e.g., strong inorganic acid mists); our incomplete knowledge of occupational carcinogens, and the use of current exposure prevalence data (SUMER 1994), which might underestimate past exposure. The SUMER survey was repeated in 2002–3: estimates of prevalence of exposures differ from those reported in the 1994 survey essentially because of lower specificity in the definition of exposure. Because exposure data used in the present study should preferably refer to the year 1985, it is more logical to use the data from the 1994 survey than those from 2002–03. In the case of obvious underestimation in the SUMER 1994 survey of the numbers of workers exposed in the past (e.g., asbestos, wood dust), we used alternative approaches to estimate numbers of workers exposed to these agents. Exposure to benzene has also greatly decreased over time, but the rather short latency period between exposure to benzene and leukaemia (around 5 to 7 years) justifies the use of exposure data from the mid-1990s.

In the case of asbestos, benzene, leather dust and wood dust, the prevalence of exposure has also been calculated among 8372 male controls included in a database managed at the InVS (unpublished data, Département Santé Travail de l'InVS). Analysis of the InVS database resulted in estimates of exposure prevalence in 1985 to asbestos and leather dust comparable to those derived from the SUMER 1994 study, while prevalence of exposure to benzene was higher, which is explicable by the secular trend in exposure to this agent.

However, our estimates might be higher than the real levels because (i) we added together the cases attributable to different exposures, neglecting the fact that the same workers may have been exposed to several carcinogens; (ii) the RRs, largely derived from studies conducted in the past when exposures were generally higher, may not be relevant to the exposure circumstances determining the current burden of cancer; and (iii) potential confounding by smoking and other factors was not properly controlled for in many studies.

Other limitations to our estimates, of which the effects on the results are less clear, include the limited quality of the exposure data and the fact that RRs were mostly derived from studies conducted in the USA and the United Kingdom and referred mainly to men, with very few data for women.

Our overall estimate of cancers attributable to occupation is somewhat lower than those reported by other authors (summarized in Table B4.5 for total cancers, lung cancer and bladder cancer among men). Methodological differences in calculation of AFs account for most of the differences in results between studies. Previous estimates based on an approach similar to the one we adopted resulted in AFs similar to ours (Dreyer et al., 1997; Driscoll et al., 2005). Other studies listed in Table B4.5 are likely to have resulted in overestimation of the burden of occupational cancer for several reasons.

First, considering as certainly carcinogenic a number of exposures that have been found to increase the risk of cancer in a few studies (e.g., Vineis and Simonato, 1991) is questionable, as there may be

many other negative studies and one may be selecting a false positive result. A more appropriate approach is to restrict the study to established carcinogenic exposures (e.g., IARC Group 1 carcinogens).

Second, selecting among many publications a high relative risk associated with an exposure because it is statistically significant (e.g., Nurminen and Karjalainen, 2001) will also bias the results. The correct approach is to use relative risks from a meta-analysis of all available data, which would also take publication bias into account.

Third, transferring an attributable fraction estimated in one country to another country assumes that the prevalence of exposure used for a given level of risk associated with that exposure is the same in both countries. The best approach is to recalculate attributable fractions using local prevalence of exposure, as far as possible.

Fourth, levels of exposure encountered in studies that revealed relative risks associated with carcinogenic agents were generally (much) higher than levels of exposure encountered in most working places, especially during the most recent years. In this respect, calculation of AFs should avoid including in the formulae figures on exposure prevalence and on RR obtained from studies involving qualitatively and quantitatively different exposures.

Lastly, it is plausible that some of the previous estimates, including those by Doll and Peto (1981), reflected the situation of developed countries in the 1980s, when the effect of heavy exposures experienced by workers in the earlier part of the 20th century was still present.

An example of problems with the assessment of the burden of occupational cancer is provided by the asbestos–mesothelioma story. Estimates of mesothelioma cases in this study do not reflect the sharp increase in mesothelioma incidence occurring in populations exposed to asbestos during their professional life before 1997. Most exposure to asbestos took place between 1950 and 1990, and there is a lag-time of about 30 years between exposure and mesothelioma occurrence. Hence, it is expected that the peak of the mesothelioma epidemic will be reached around 2020–2030. According to one model, predicted annual mesothelioma deaths in French men will be in the range 1140 to 1300 between 2026 and 2043 (Banaei et al., 2000), while another model predicts that in 2020, there will be around 1040 mesothelioma deaths in French males and 115 in French females (Ilg et al., 1998). After 2030, with decreasing numbers of subjects who were exposed before 1997, the mesothelioma incidence is expected to decline steadily to a very low level, with probably only a few cases per year in 2060. Industrial use of asbestos represents one of the most dramatic cancer epidemic episodes induced by human activity in France and elsewhere, but estimation of the fraction of mesothelioma attributable to asbestos exposure and accurate prediction of the future course of the mesothelioma epidemic is challenging for the following reasons:

1. The term “asbestos” encompasses two main types of silicate fibres, i.e., chrysotile and amphiboles. The latter type of fibre has a greater capacity to induce mesothelioma, but the fibre type is unknown for most of the asbestos that was imported into France.
2. Most studies on exposure to asbestos were performed in the 1990s, and retrospective assessment based on past professional history could provide at best a likelihood of having been exposed to asbestos, without good estimates of dose or fibre type.
3. Before 1980, diagnosis of mesothelioma was not always based on biopsy evidence. In France, few local cancer registries were in operation at that time and the evidence on the first phases of the mesothelioma epidemic comes mainly from death certificates, on which diagnoses of mesothelioma are prone to error.
4. Before 1990, classification of pleural cancer in cancer registries was imprecise, and many epidemiological studies referred to pleural cancer, an entity that could encompass cancers different from mesothelioma, e.g., pleural metastasis of another cancer, pleural extension of a lung cancer, pleural involvement of haemato-lymphatic cancer. It has been estimated that in France, 81% of “pleural cancers” were mesothelioma (Banaei et al., 2000).
5. In the 1990s, few deaths from mesothelioma were reported in younger age groups (i.e., < 50 years old). Consequently, considerable random variation affects predictions of mortality from mesothelioma in younger age groups.
6. Data both on exposures to asbestos and on

mesothelioma mortality in women are less reliable and precise than in men.

7. Knowledge of past asbestos exposure may influence the accuracy of the diagnosis of mesothelioma.

References

Banaei A, Auvert B, Goldberg M, et al. Future trends in mortality of French men from mesothelioma. Occup Environ Med 2000;57:488–494.

Berrino F, Richiardi L, Boffetta P, et al. Occupation and larynx and hypopharynx cancer: a job-exposure matrix approach in an international case-control study in France, Italy, Spain and Switzerland. Cancer Causes Control 2003;14:213–223.

Boffetta P; Jourenkova N, Gustavsson P. Cancer risk from occupational and environmental exposure to polycyclic aromatic hydrocarbons. Cancer Causes Control 1997;8:444–472.

Cogliano V, Grosse Y, Baan R, et al. Advice on formaldehyde and glycol ethers. Lancet Oncol 2004;59:528.

Demers PA, Boffetta P, Kogevinas M, et al. Pooled reanalysis of cancer mortality among five cohorts of workers in wood-related industries. Scand J Work Environ Health 1995;21:179–190.

Direction des Relations du Travail. Conditions de travail, Bilan 2002. Ministère des Affaires Sociales, du Travail et de la Solidarité.

Dreyer L, Andersen A, Pukkala E. Occupation. Acta Pathol Microbiol Immunol Scand 1997;105 Suppl 76:68–79.

Driscoll T, Nelson DI, Steenland K, et al. The global burden of disease due to occupational carcinogens. Am J Ind Med 2005;48:419–431.

Doll, R, Peto, R. The Causes of Cancer. Oxford, Oxford University Press, 1981.

Doll R, Peto R. Epidemiology of cancer. In: Oxford Textbook of Medicine, 4th edition, Oxford, Oxford University Press, 2005.

Goldberg M, Imbernon E, Rolland P, et al. The French National Mesothelioma Surveillance Program. Occup Environ Med 2006;63:390–395.

Goodman M, Morgan RW, Ray R, et al. Cancer in asbestos-exposed occupational cohorts: a meta-analysis. Cancer Causes Control 1999;10:453–465.

Hayes RB. The carcinogenicity of metals in humans. Cancer Causes Control 1997;8:371–385.

Ilg AGS, Bignon J, Valleron AJ. Estimation of the past and future burden of mortality from mesothelioma in France. Occup Environ Med 1998;55:760–765.

Imbernon E. Estimation du nombre de cas de certains cancers attribuables à des facteurs professionnels en France. Paris, Institut de veille sanitaire, 2003.

INRS. Institut National de Recherche et de Sécurité. Cahiers de notes documentaires No. 186. Hygiene et securite du travail, 2002.

International Agency for Research on Cancer. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Vol. 47. Some Organic Solvents, Resin Monomers and Related Compounds, Pigments and Occupational Exposures in Paint Manufacture and Painting. Lyon, IARC; 1989

Iwatsubo Y, Pairon JC, Boutin C, et al. Pleural mesothelioma: dose-response relation at low levels of asbestos exposure in a French population-based case-control study. Am J Epidemiol. 1998;148:133–142.

Kogevinas M, Sala M, Boffetta P, et al. Cancer risk in the rubber industry: a review of the recent epidemiological evidence. Occup Environ Med 1998;55:1–12.

Kubasiewicz M, Starzy_ski Z, Szymczak W. Case-referent study on skin cancer and its relation to occupational exposure to polycyclic aromatic hydrocarbons. II. Study results. Pol J Occup Med Environ Health. 1991;4:141–147.

Lynge E, Anttila A, Hemminki K. Organic solvents and cancer. Cancer Causes Control. 1997;8:406–419.

't Mannetje A, Kogevinas M, Luce D, et al. Sinonasal cancer, occupation, and tobacco smoking in European women and men. Am J Ind Med. 1999;36:101–107.

Ministère du Travail. 'Bilans annuels sur les Conditions de Travail (2000–2005) Direction des relations du Travail, Conseil Supérieur de la Prévention des Risques Professionnels, 2006.

Nurminen M, Karjalainen A. Epidemiologic estimate of the proportion of fatalities related to occupational factors in Finland. Scand J Work Environ Health 2001;27:161–213.

Robé MC, Tirmarche M. Radon dans les bâtiments; Collection «les techniques de l'ingénieur». C3 384-année 2003. Institut de Radioprotection et de Sûreté Nucléaire (IRSN).

Rogel A, Laurier D, Tirmarche M, Quesne B. Lung cancer risk in the French cohort of uranium miners. J Radiol Prot 2002;22 (3A):A101–106.

Sénat 2005. Rapport d'Information No. 37. Annexe au procès-verbal de la séance du 20 octobre 2005. Paris, 2005.

Siemiatycki J, Richardson L, Straif K, et al. Listing occupational carcinogens. Environ Health Perspect

2004;112:1447–1459.

Steenland K, Mannetje A, Boffetta P, et al. Pooled exposure-response analyses and risk assessment for lung cancer in 10 cohorts of silica-exposed workers: an IARC multicentre study. Cancer Causes Control 2001;12:773–784.

Steenland K, Burnett C, Lalich N, et al. Dying for work: the magnitude of US mortality from selected causes of death associated with occupation. Am J Ind Med 2003;43:461–482.

SUMER 1994. http://www.travail.gouv.fr/etudes-recherche-statistiques/statistiques/sante-au-travail/87.html

UNSCEAR : United Nations Scientific Committee on the Effects of Atomic Radiation Sources, effects and risks of ionising radiation. Report to the General Assembly, with Annexes. United Nations, New York 2000

Vineis P, Simonato L. Proportion of lung and bladder cancers in males resulting from occupation: a systematic approach. Arch Environ Health 1991;46:6–15.

Vineis P, Pirastu R. Aromatic amines and cancer. Cancer Causes Control. 1997;8:346–355.

Table B4.1 - Relative risks used in the analysis of occupational exposures

Exposure	Cancer	RR	Reference
Asbestos	Mesothelioma	*	–
	Lung	1.48	Goodman et al., 1999
Polycyclic aromatic hydrocarbons, combustion fumes, tar and pitch	Lung	1.37 §	Boffetta et al., 1997
	Laryngeal	1.38 §	
	Bladder	1.40 §	
Chromium VI	Lung	3.10 §	Hayes, 1997
	Sinonasal	5.18 §	
Painters	Lung	1.29 §	IARC, 1989
Nickel	Lung	1.80 §	Hayes, 1997
	Sinonasal	2.09 §	
Benzene	Leukaemia	3.30 §	Lynge et al., 1997
Rubber industry	Bladder	2.40 §	Kogevinas et al., 1998
	Leukaemia	1.30 §	
Silica	Lung	1.20	Steenland et al., 2001
Aromatic amines	Bladder	1.60 §	Vineis and Pirastu, 1997
Radon	Lung	*	–
Boot and shoe manufacture and repair. Leather dust.	Sinonasal	1.92 men 2.71 women	t'Mannetje et al., 1999
Wood dust	Sinonasal	*	–
Cadmium	Lung	1.17 §	Hayes, 1997
Untreated and mildly treated mineral oils	Skin, squamous cell carcinoma	1.46	Kubasiewicz et al., 1991

* AF calculated directly, see text

§ Estimated for the present study, on the basis of reviews quoted in the references

Table B4.2 – Prevalence of lifetime occupational exposure in France

Agent	Men		Women		Reference
	N*	%	N*	%	
Asbestos	–	9.1	§		Iwatsubo et al., 1998
Polycyclic aromatic hydrocarbons, combustion fumes, tar and pitch	303	8.36	23	0.78	SUMER 1994§
Chromium VI	42	1.16	9	0.30	SUMER 1994
Painters	–	2.00	†		Berrino et al., 2003‡
Nickel	23	0.63	23	0.78	SUMER 1994
Benzene	61	1.68	5	0.17	SUMER 1994
Rubber industry	–	1.10	†		Berrino et al., 2003‡
Silica	85	2.35	11	0.37	SUMER 1994
Aromatic amines	22	0.61	13	0.44	SUMER 1994
Radon	–	–	–	–	See text ¶
Leather dust	–	2.70	–	2.70	Berrino et al., 2003‡
Wood dust II	–	–	–	–	See text ¶
Cadmium	8	0.22	2	0.07	SUMER 1994
Untreated and mildly treated mineral oils	490	4.96	32	0.40	SUMER 1994 #

* Numbers (_1000) derived from the SUMER study in 1994. The SUMER study of 1994 covers only 7 000 000 active male workers and 5 000 000 active female workers, mostly employed in the private sector

† Data on prevalence of exposure not available; assumed to be zero

‡ Prevalence of exposure among controls, not shown in original article and directly obtained from F. Berrino, personal communication

§ For women we used the ratio of the number of lung cancers to mesotheliomas from men, see text

II AF calculated directly – see text

¶ See text for details of calculation of occupational exposure prevalence

SUMER 94 data refer to all mineral oils. A factor of 37%, estimated from INRS data (2002), was applied to all mineral oil exposure to estimate prevalence

Table B4.3 –Numbers of cancer cases and deaths attributable to occupation in France, by sex, for the year 2000

Exposure	Cancer	Men			Women		
		AF%	Cases	Deaths	AF%	Cases	Deaths
Asbestos	Mesothelioma	83.2	558	504	38.4	77	62
	Lung	4.2	969	862	2.9	133	108
Polycyclic aromatic hydrocarbons, combustion fumes, tar and pitch	Larynx	3.1	120	53	0.3	1	0
	Lung	3.0	697	619	0.3	13	12
	Bladder	3.2	287	104	0.3	5	3
Chromium (VI)	Nose and sinuses	4.6	21	5	1.3	2	1
	Lung	2.4	550	489	0.6	29	27
Painters	Lung	0.6	134	119	*		
Nickel	Nose and sinuses	0.7	3	1	0.8	1	0
	Lung	0.5	117	104	0.6	28	26
Benzene	Leukaemia	3.7	135	100	0.4	10	9
Rubber industry	Bladder	1.5	136	49	*		
	Leukaemia	0.3	12	9	*		
Silica	Lung	0.5	108	96	0.07	3	3
Aromatic amines	Bladder	0.4	33	12	0.3	5	3
Radon	Lung	0.1	26	23	–	–	–
Leather dust	Nose and sinuses	2.4	11	2	4.4	7	2
Wood dust	Nose and sinuses	19.2	87	19	*		
Cadmium	Lung	0.04	9	8	0.011	0	0
Mineral oils	Skin SCC †	2.2	– ‡	5	0.1	–	–
Any exposure in Table	Cancers in Table		4013	3183		314	256
% of all cancers §			2.5%	3.7%		0.3%	0.5%

* AF was not calculated because data on prevalence of exposure were not available.

† Squamous cell carcinoma.

‡ Incidence data not available.

§ These totals do not take into account interactions between occupational factors. Interactions are known to be of low magnitude (see Section C2), and totals should thus be slightly lower

Table B4.4 - Numbers of cancer deaths attributable to occupational exposures, by type of cancer in 2000

Cancer	Men		Women	
	AF%	Deaths	AF%	Deaths
Lung	11.3	2320	4.2	177
Mesothelioma	83.2	504	38.4	62
Bladder	5.1	165	0.6	6
Leukaemia	4.1	109	0.4	9
Larynx	3.1	53	0.3	0
Nasal sinus	27.0	27	6.5	3
Skin	2.2	5	0.1	0
All cancers	3.7	3183	0.5	258

Table B4.5 - Estimates of the fraction of selected cancers among men attributable to occupation

					Attributable fraction		
Reference	**Population**	**Method**	**Indicator**	**Sex**	**All cancers**	**Lung**	**Bladder**
Estimates based on relative risks and data on prevalence of exposure							
Dreyer et al., 1997	Nordic countries	Relative risk from review of literature, prevalence of exposure from national surveys	Incidence	Men	3%	13%	2%
Driscoll et al., 2005	Western Europe	Average relative risk for eight carcinogens, prevalence of exposure from international data	Mortality	Men	NA	10%	NA
Present study	France	Relative risk from meta-analyses, prevalence of exposure mostly from national surveys	Mortality	Both	2.4%	10.1%	4.0%
				Men	3.7%	11.3%	5.1%
Estimates based on qualitative review of the literature							
Doll and Peto, 1981	USA	Critical review of literature	Mortality	Both	4.2%	12.5%	8.4%
				Men	6.8%	15%	10%
Vineis and Simonato, 1991	Various populations	Review of individual studies	Incidence, mortality	Men	NA	1–40%	0–24%
Nurminen and Karjalainen, 2001	Finland	Includes suspected carcinogens and false positive results; likely overestimation of exposure prevalence	Incidence, mortality	Men	13.8%	29.0%	14.2%
Imbernon, 2002	France	Attributable fraction from literature	Incidence, mortality	Men	NA	13–29%	10–21.5%
Steenland et al., 2003	USA	Attributable fraction from literature	Mortality	Men	NA	6.1–17.3%	7–19%
Doll and Peto, 2005	United Kingdom	Review of literature	Mortality	Both	2.0%	NA	NA
NA, not available							

Section B5: Obesity and overweight

1. Definition of exposure

The body mass index (BMI) is the weight (in kg) divided by the square of the height (in metres) of an individual. According to international standards, male and female adults with a body mass index (BMI) between 25 and 29.9 kg/m2 are considered overweight, while if their BMI is equal to or greater than 30 they are obese.

Overweight and obesity represent risk factors of considerable importance for cardiovascular diseases, diabetes mellitus and arthrosis. An IARC working group found that these factors were consistently associated with the cancers listed in Table B5.1 (IARC, 2002). This systematic review concluded that there was not sufficient evidence for an association of overweight or obesity with prostate or gallbladder cancer.

The alternative scenario taken for calculation of AF is that of absence (i.e., zero prevalence) of overweight and obesity.

2. Data used for RR estimates

We used data from a meta-analysis by Bergstrom et al. (2001) (Table B5.1), that can be used for both males and females. Because the evidence for an effect of obesity and overweight for breast cancer is limited to postmenopausal women (IARC, 2002), we applied the attributable fraction to incidence and mortality of breast cancer occurring after 49 years old.

3. Data used for exposure prevalence

We used surveys conducted by the INSEE in the general population ≥ 20 years of age in 1980 and 1991 and analysed by Maillard et al. (1999). In these surveys, samples of 6792 men and 7150 women in 1980, and 7250 men and 7856 women in 1991 were asked to self-report their weight and height. Maillard et al. made a direct adjustment of prevalences in 1991 on the age distribution of 1980. We calculated crude prevalences of overweight and obesity in 1980 and 1991 by taking the prevalences displayed in Figure 1 of Maillard et al. (1999) and applying them to the 1980 and 1991 French male and female populations (data from the Institut national d'études démographiques (INED)). We then recalculated the numbers of overweight and obese males and females per 10-year age group and thence derived the prevalence in 1980 and 1991 for males and females 20 years of age and older (Table B5.2). To estimate the 1985 proportions of overweight and obesity, we performed a linear interpolation between the 1980 and 1991 data (Table B5.2 and Figure B5.1). For breast cancer, we made these interpolations only for women aged 50 years and older.

4. Calculation of AFs

Calculations of attributable fractions for cancer incidence and mortality are summarized in Table B5.3. Overweight and obesity are involved in a greater proportion of cancers in females, essentially because of their role in endometrial and breast cancer.

5. Discussion

The results of the INSEE surveys in 1991 are quite similar to those from a study conducted in 1988 (Laurier et al., 1992) in subjects 16–50 years old, but with obesity reported as BMI ≥ 29 kg/m2 in men and ≥ 27.5 kg/m2 in women. More recent INSEE data from surveys in 2003 on 21 000 adults 18 years old or more (using self-reported weight and height) show increasing obesity in both sexes, but a decrease in overweight in both sexes (Figure B5.1).

The ObEPI surveys performed in 1997, 2000 and 2003 used self-reported data on weight and height of subjects 15 years of age and older included in a sample representative of the French population (25 770 subjects in 2003) (Charles et al., 2002; ObEPI,

2003). These surveys show an increase in obesity (both sexes combined) similar to those reported in the INSEE surveys (Figure B5.2). There is, however, a divergence between INSEE and ObEPI surveys in the trends in overweight, with a steady increase in ObEPI surveys, but a decrease in the INSEE surveys. Other data from selected populations, but using measured weight and height data (and not self-reported weight and height) indicate sustained increases in overweight and obesity in the French population (Salem et al., 2006), and suggest that the INSEE data are somewhat biased towards underestimation of height and weight reported by interviewees.

In most industrialized countries, overweight and obesity are increasing, which will contribute to steadily increasing numbers of several cancers in the future. In the coming decades, if there is no reversal in the currently observed trends, obesity and overweight will significantly contribute to further increases in cancer incidence.

References

Bergstrom A, Pisani P, Tenet V, et al. Overweight as an avoidable cause of cancer in Europe. Int J Cancer. 2001;91:421–30. Erratum in: Int J Cancer 2001;92:927.

Charles MA, Basdevant A, Eschwege E. Prévalence de l'obésité de l'adulte en France. La situation en 2000. A partir des résultats des études OBEPI. Ann. Endocrinol, 2002;63, 2, Cahier 1, 154–158

International Agency for Research on Cancer. IARC Handbooks of Cancer Prevention, Vol. 5, Weight Control and Physical Activity. Lyon: IARC; 2002.

Lanoë JL, Dumontier F. Tabagisme, abus d'alcool et excès de poids. INSEE Première, N° 1048, Novembre 2005.

Laurier D, Guiget M, Chau NF, et al. Prevalence of obesity: a comparison survey in France, the UK and the US. Int J Obesity 1992;16:565–572.

Maillard G, Charles MA, Thibult N, et al. Trends in the prevalence of obesity in the French adult population between 1980 and 1991. Int J Obes Relat Metab Disord 1999;23:389–394.

ObEPI. Communiqué de presse: Résultats de l'enquête ObEpi 2003 sur l'obésité et le surpoids en France. Paris, Institut Roche de l'Obésité, 2003.

Salem G, Rican S, Kurzinger ML. Atlas de la Santé en France. Vol. 2: Comportements et maladies. Paris, John Libbey Eurotext, 2006.

Table B5.1 – Summary RRs of cancers associated with overweight and obesity*

Cancer site §	Overweight	Obesity
Oesophagus (adenocarcinoma)	2.00	2.00
Colon-rectum	1.15	1.33
Kidney	1.36	1.84
Corpus uteri	1.59	2.52
Breast in postmenopausal women	1.12	1.25

* From Bergstrom et al., 2001

§ From IARC, 2002.

Table B5.2 – Prevalence of overweight and obesity in France in 1985

(Maillard et al.; 1999, adapted as outlined in text)

		Prevalence	
	Year	**Males**	**Females**
BMI = 25–29.9	1980	32.4%	20.1%
	1991	33.7%	20.3%
BMI ≥ 30	1980	6.2%	6.1%
	1991	6.3%	6.9%
BMI = 25–29.9	1985 §	33.0%	20.2% (29.2%*)
BMI ≥ 30	1985 §	6.3%	6.4% (9.6%*)

* Only for women ≥ 50 years old

§ Prevalence in 1985 was estimated by linear interpolation of prevalence in 1980 and 1991

Table B5.3 – Numbers of cancer cases and deaths attributable to obesity and overweight in France in the year 2000

Cancer	Men			Women		
	AF%	Cases	Deaths	AF%	Cases	Deaths
Oesophagus* (adenocarcinoma)	28.2%	200	172	21.0%	68	51
Colon-rectum	6.6%	1273	547	4.8%	826	373
Kidney	14.6%	776	276	11.3%	336	125
Corpus uteri	–	–	–	17.8%	904	243
Breast over 50 years	–	–	–	5.6%	1766	529
All cancers	1.4%/1.1%§	2249	995	3.3%/2.3%§	3900	1321

* See section on Methods for details on estimation of oesophageal adenocarcinoma

§ AF for incidence/mortality

Figure B5.1 –Trends in overweight and obesity in adults (18+) in France 1980-2003
(Data INSEE in Maillard et al., 1999 and Lanoël and Dumortier 2005)

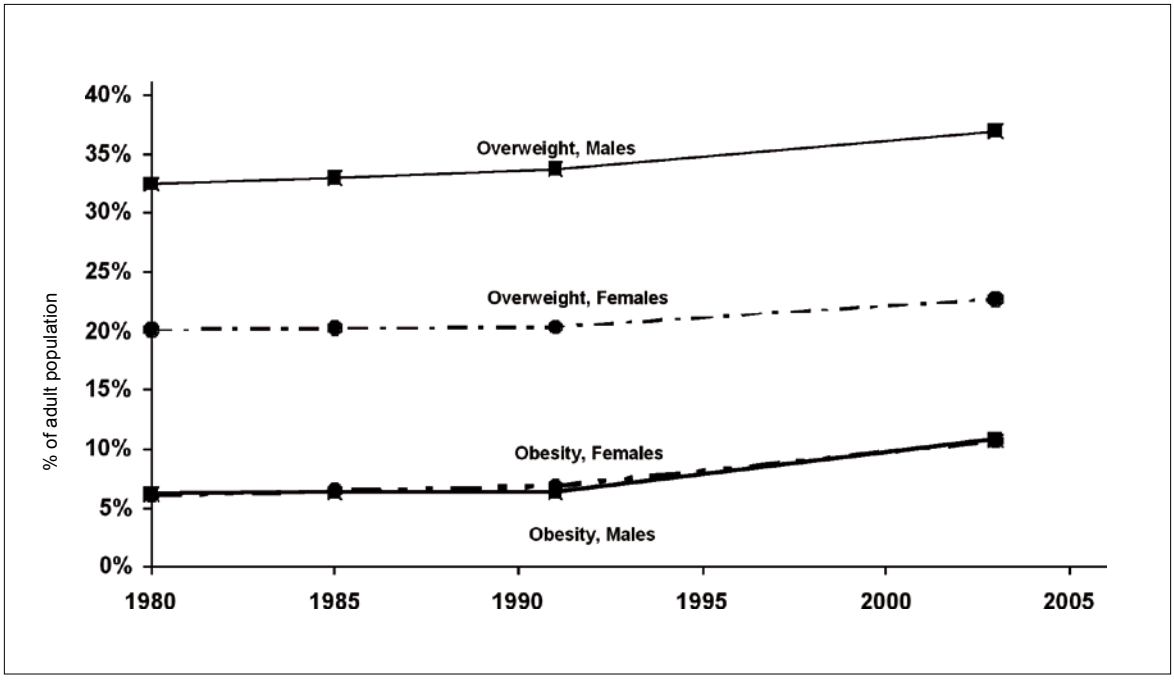
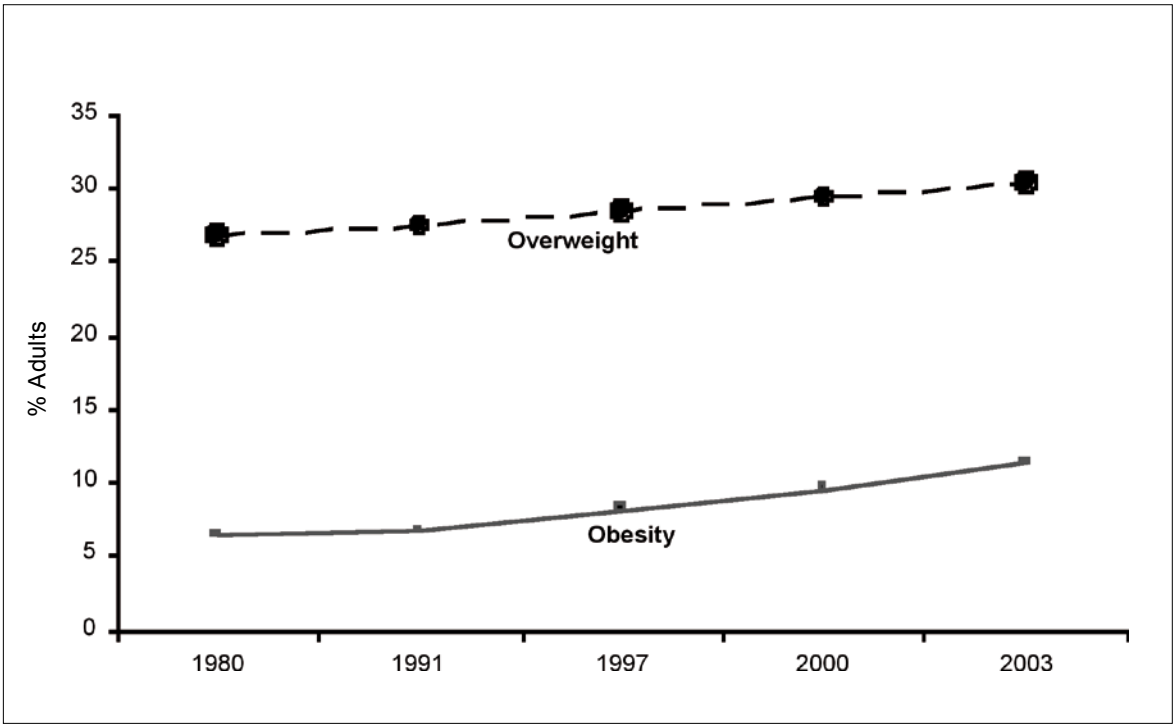


Figure B5.2 – Prevalence of overweight (BMI: 25-29.9) and obesity (BMI: 30+) in France in both sexes
(Data for 1980 and 1991 from INSEE, compiled by Maillard et al, 1999; data for 1997, 2000 and 2003 from ObEPI surveys, Charles et al., 2002 and ObEPI 2003)



Section B6 : Physical inactivity

1. Definition of exposure

The evidence for a cancer-preventive effect of physical activity was evaluated by an IARC working group (IARC, 2002) which concluded that "there is sufficient evidence in humans for a cancer-preventive effect of physical activity" for cancers of the colon and breast, and preventive effects increase with increasing physical activity in terms of duration and intensity. This protective effect was independent of the effect of body weight.

Conversely, physical inactivity is a risk factor for cancer. We took as alternative exposure scenarios indicators related to "vigorous recreational physical activity".

2. Data used for RR estimates

The RR of breast cancer associated with physical inactivity was computed from the RR reported by the French E3N cohort study (Tehard et al., 2006). This cohort included 98 995 women, insured with the "Mutuelle Générale de l'Education Nationale", aged 40 to 65 years at inclusion and followed for an average of 11.4 years. Since the IARC evaluation was based on studies of recreational physical activity, we took the RR reported in the study for vigorous recreational activity.

The RRs we used for calculating an AF had to correspond to the exposure data that could be considered as most representative of physical inactivity in France, i.e., results from a European survey (Vaz de Almeida et al., 1999 – see next sub-section for a description). The two published tables from which we derived RRs and exposure data are :

Excerpt 1: from Table 3 of Tehard et al., 2006

Vigorous recreational activity (h/wk)	Cases	Total person-years	Multivariate adj. RR	Weight used for RR estimate
Inactive†	668	175 292	1.00 (reference)	17.5
0	1097	319 096	0.90 (0.81–0.99)	17.5
[1–2]	845	258 953	0.88 (0.79–0.97)	2
[3–4]	238	78 163	0.82 (0.71–0.95)	31.5
≥ 5	93	38 082	0.62 (0.49–0.78)	31.5

† Women who reported no moderate nor vigorous recreational activity were considered as "inactive"

Excerpt 2: from Table 5 of Vaz de Almeida et al., 1999
Table. Percentage of EU subjects in the different categories of time dedicated to leisure-time physical activity (number of hours per week) classified by sex

Sex	None	< 1.5 h	1.5–3.5 h	> 3.5 h
Male	28	2	7	64
Female	35	2	9	54

We used as the "at risk category" in Excerpt 1 the inactive women and women with zero vigorous recreational activity. We used as a referent category women who had one or more hours per week of vigorous activity.

In order to take into account the levels of physical activity described in Europe, we computed weights for the relative importance of each category of physical activity reported by Vaz de Almeida et al. (1999) (Excerpt 2). These weights are displayed in the right-hand column of Excerpt 1. The RRs of Excerpt 1 were transformed into their napierian logarithm equivalent, i.e., ln(RRs), and applying the weights on these ln(RRs), we computed a pooled RR of breast cancer associated with physical inactivity of 1.32 (95% CI 1.06–1.64) compared with physically active women in the general population.

The RR of colon cancer associated with physical inactivity was extracted from a recent meta-analysis (Samad et al., 2005), which showed a significant protective effect of physical activity during leisure periods. Because different metrics were used in the publications included in the meta-analysis, the author only presented estimates of RRs for "physical activity" without categories. Based on 19 cohorts, the combined RRs of colon cancer were 0.79 for men and 0.71 for women. We used the reverse of this estimate as the risk of colon cancer associated with physical inactivity. We found no data on physical activity and rectal cancer.

Table B6.1 summarizes the RRs used to estimate AFs associated with physical inactivity.

3. Data used for prevalence

We used data reported from a European survey (Vaz de Almeida et al., 1999, Kearney et al., 1999) conducted in 1997 in 15 countries of the European Union. This survey was conducted on a sample of 15 239 individuals (7467 men and 7772 women) aged 15 years and older. For each country, quotas on age and sex were used to obtain representative samples. Results on physical inactivity by gender were only reported for the 15 countries. We applied these proportions of prevalence of physical inactivity in Europe to France, as in the European survey, rates of physical inactivity in France did not differ from the European average. Twenty eight per cent of men and 35% of women reported not having spent any time on physical activity during leisure periods (Table B6.2).

4. Calculation of AFs

Table B6.2 reports the AFs and the attributable numbers of cancer cases and deaths for the year 2000. A total of 780 cases among men (0.5% of the total) and 5541 cases among women (4.7% of the total) were attributable to physical inactivity in France in 2000. For women, around 75% are breast cancers. Physical inactivity is associated with 427 cancer deaths (0.5% of all cancer) in men and 1812 cancer deaths (3.2% of all cancers) in women.

5. Discussion

A survey by the Institut National de Prévention et d'Education pour la Santé (INPES) in 2005 among 30 514 adults 18–65 years of age suggested a proportion of 33% of physically inactive adults in France (INPES, Baromètre Santé, 2005). This estimate is close to the figures that we used from the European survey.

Additional data on the prevalence of physical activity were reported in 1997 (Steptoe et al., 1997) from a European survey conducted in 1989–1992. However, this survey was conducted on university students aged 18–30 years who could not be considered as representative of the French population. The prevalence of physical inactivity in the European survey is higher than that reported in the French cohort study E3N cohort, exclusively of women (Tehard et al., 2006). Only 20.2% of the E3N subjects were categorized as "inactive". However, it is probable that more active women were more willing than less active women to participate in a long-term cohort study. Furthermore, prevalence of physical activity is directly correlated with education level and the majority of women in the E3N cohort had a high education level.

To the best of our knowledge, no study has yet tried to estimate the optimal level of physical activity for cancer prevention. However, for colon cancer, the IARC working group on physical activity noted that "at least 30 minutes per day of more than moderate level of physical activity might be needed to see the greatest effect in risk reduction" (IARC, 2002). For breast cancer, the "risk reduction begins at levels of 30–60 minutes per day of moderate-intensity to vigorous activity in addition to the usual levels of

occupational and household activity of most women" (IARC, 2002). In view of these conclusions, it is probable that low or moderate physical activity does not reduce the risks of colon or of breast cancer.

References

Kearney JM, Kearney MJ, McElhone S, Gibney MJ. Methods used to conduct the pan-European Union survey on consumer attitudes to physical activity, body weight and health. Public Health Nutrition 1999;2(1a):79–86.

INPES. Institut National de Prévention et d'Education pour la Santé. Baromètre Santé 2005.

International Agency for Reasearch on Cancer. IARC Handbooks of Cancer Prevention, Vol. 5, Weight Control and Physical Activity. Lyon: IARC; 2002.

Samad AKA, Taylor RS, Marshall T, Chapman MAS. A meta-analysis of the association of physical activity with reduced risk of colorectal cancer. Colorectal Disease 2005;7:204–213.

Steptoe A, Wardle J, Fuller R, et al. Leisure-time physical activity exercise: prevalence, attitudinal correlates, and behavioral correlates among young Europeans from 21 countries. Prev Med 1997;26:845–854.

Tehard B, Friedenreich CM, Oppert JM, Clavel-Chapelon F. Effect of physical activity on women at increased risk of breast cancer: results from the E3N cohort study. Cancer Epidemiol Biomarkers Prev 2006;15:57–64.

Vaz de Almeida MD, Graca P, Afonso C, et al. Physical activity levels and body weight in a nationally representative sample in the European Union. Public Health Nutrition 1999;2(1a):105–113.

Table B6.1 – Prevalence of physical inactivity in French adults and associated RR

Cancer	Sex	% inactivity	RR	95% CI	
Colon	Men	28%	1.27	1.10	1.47
	Women	35%	1.40	1.13	1.74
Breast	Women	35%	1.32	1.06	1.64

Table B6.2 – Numbers of cancer cases and deaths attributable to lack of physical activity in France, by sex, for the year 2000

Cancer	Men			Women		
	AF%	Cases	Deaths	AF%	Cases	Deaths
Colon	7%	780	427	12.3%	1304	703
Breast	–			10.1%	4237	1109
Total		780	427		5541	1812
% all cancer		0.5%	0.5%		4.7%	3.2%

Section B7: Hormone replacement therapy and oral contraceptives

I. Hormone replacement therapy (HRT)

Hormone therapy (HRT) for women consists in the use of pharmaceutical products containing estrogens (E) alone or a combination of estrogens and progestogens (E+P), regardless of regimen and route of administration.

1. Context

HRT has been promoted for alleviation of symptoms of menopause, or after menopause for the presumed beneficial effects of these hormones on various health conditions such as cardiovascular disease and osteoporosis. In the 1990s, it was discovered that E alone increased the risk of endometrial cancer and slightly increased the risk of breast cancer. HRT was then shifted to E+P formulations.

In 1997, a large collaborative study conducted a meta-analysis of all observational studies (mainly case–control studies) on HRT and breast cancer, showing evidence for a positive association between HRT and breast cancer when HRT use lasted for five years or more (CGHFBC, 1997). The effects of HRT on breast cancer risk were present for current HRT users but ceased for women who had stopped taking HRT five years previously or more. Other studies reported other side-effects of HRT such as deep vein thrombosis, and questioned the putative cardiovascular benefits of HRT use.

At the end of the 1990s, two large-scale randomized placebo-controlled trials in the USA, the HERS and HERS II trials (Hulley et al., 2002) and the Women's Health Initiative (WHI) trial (Rossouw et al., 2002; Chlebowski et al., 2003; Anderson et al., 2004) were initiated to try to answer the numerous puzzling questions regarding HRT use and various health conditions. Both the HERS II and WHI trials demonstrated that women taking E+P had a higher risk of breast cancer, myocardial infarctions, cardiovascular diseases, deep venous thrombosis, stroke and decline of cognitive functions. Reduced risks for fractures and colorectal cancer were found when E+P was taken for five years or more. E+P did not affect endometrial cancer incidence or all-cause mortality. Trials with E alone reached similar conclusions except for breast cancer, for which, unexpectedly, the WHI trial found a reduced risk (Anderson et al., 2004). The overall conclusion of the WHI trials was that increased disease risks associated with the use of E or of E+P largely outweigh the benefits.

Simultaneously with the HERS II and WHI trials, ten cohort studies were conducted on HRT use and cancer risk (Table B7.1). Seven of these studies were conducted in the Nordic countries (Jernström et al., 2003; Olsson et al., 2003; Persson et al., 1999; Stahlberg et al., 2004; Tjønneland et al., 2004; Bakken et al., 2004; Ewertz et al., 2005), one was conducted in the USA (Schairer et al., 2000), one in the UK – the Million Women Study (MWS) (Million Women Study Collaborators, 2003), and a tenth in France (Fournier et al., 2005a). The main results from these cohort studies are displayed in Table B7.1. The seven Nordic cohorts reported breast cancer risks associated with HRT use (E or E+P) mostly higher than those from the MWS (2003). The French E3N cohort (Fournier et al., 2005a, 2007) yielded relative risks associated with four or more years of E+P use not very different from those found by the MWS and several Nordic studies.

The largest cohort study was the MWS conducted

in the UK (Million Women Study Collaborators, 2003). The MWS included 1 084 110 women between 50–64 years old who were participants in the National Health Service Breast Cancer Screening Programme, half of whom had used HRT. 9364 incident cases of breast cancer were registered during follow-up. Overall, compared with women not using HRT, the breast cancer risk was multiplied by 1.30 (95% CI 1.22–1.38) for current users of E formulations, and by 2.00 (95% CI 1.91–2.09) for current users of E+P formulations. Because of its high statistical power, the Million Women Study was also able to assess the risk of the relatively rare ovarian cancer with current HRT use (Million Women Study Collaborators, 2007). This is important since ovarian cancer is usually diagnosed at an advanced stage, at which there is no cure.

Criticisms of the MWS study (e.g., Whitehead and Farmer, 2004; Lopes, 2003; Shapiro, 2004; van der Mooren and Kenemans, 2004) pointed to methodological problems of secondary importance and never offered any plausible alternative explanation for the findings. For instance, it is sometimes claimed that the MWS had no "control group". The MWS is a cohort study, and therefore, the women who never used HRT (i.e., 50% of the entire cohort) constituted the natural control group, and breast cancer risks were calculated using women who never used HRT as the referent category (i.e., the category with no increased breast cancer risk associated with HRT use). It was also claimed that differences in age or in body mass index between HRT users and non-users could explain findings. These arguments do not hold since all risk calculations were carefully adjusted on variables that could eventually confound the association between HRT use and breast cancer, such as body mass index and age.

The IARC Monograph and the AFSSAPS report on HRT use and cancer

In view of the numerous new results published from 2000 onwards, the IARC convened a Monograph meeting on HRT and cancer risk in June 2005. Summary conclusions of this meeting were published in 2005 (Cogliano et al., 2005) and details on conclusions of the Monograph may be found at the url: http://monographs.iarc.fr/ENG/Meetings/91-menop-ther.pdf. The full printed Monograph is in press. The following excerpt from the detailed conclusions about HRT and breast cancer is accessible on the mentioned web-site: *"Two large randomized trials, 10 cohort studies and seven case–control studies reported on the relationship between the use of combined estrogen–progestogen menopausal therapy and breast cancer in postmenopausal women. The studies consistently reported an increased risk for breast cancer in users of combined estrogen–progestogen therapy compared with non-users. The increased risk was greater than that in users of estrogen alone. The available evidence was inadequate to evaluate whether or not the risk for breast cancer varies according to the progestogenic content of the therapy, or its dose, or according to the number of days each month that the progestogens are added to the estrogen therapy".* Furthermore, concerning the doses of estrogens or progestogens in HRT, *"The data are [ ] insufficient to determine whether the risk varies with type of compound or the dose of various compounds used".*

Independently from the IARC Monograph, the experts of the Agence Française de Sécurité Sanitaire des Produits de Santé (AFSSAPS) came to similar conclusions (AFSSAPS, 2004, 2006): *"Actuellement aucune donnée issue d'essais randomisés ne permet de savoir si les risques associés au traitement hormonal de la ménopause sont influencés ou non par le type d'estrogène (estrogènes conjugués équins, estradiol), ou par le type de progestatif (acétate de médroxyprogestérone, lévonorgestrel, noréthistérone, progestérone, etc.), ou par la voie d'administration de l'estrogène (orale, transdermique), ou enfin par les modalités d'utilisation du progestatif (administration séquentielle ou continue)."* (AFSSAPS, 2006, page 5).

There is thus at present no convincing evidence from laboratory or human studies that the risk of breast cancer associated with HRT use would differ according to the constituents and their dose, continuous or sequential administration, or the route of administration.

Timing and duration of HRT use

Practically all the breast cancer risk associated with HRT use is linked to current use, as opposed to past use. Past HRT use is taken to mean that use of HRT ceased at least one year previously, and current use may be defined as taking HRT in the last 12 months.

Past HRT has been associated rarely with a significant small increase in breast cancer risk.

All studies on HRT and breast cancer have shown that the risk among current HRT users increases with time since first use. Table B7.3 shows the increasing risk associated with HRT use found in the MWS (2003), with a relative risk of 2.31 after 10 years of use. HRT use for less than 12 months entails no or only low increase in breast cancer risk (MWS, 2003; CGHFBC, 1997).

The breast cancer risk associated with HRT does not persist after cessation of HRT use, and probably the risk becomes very low if not inexistent 12 months after cessation of HRT use.

HRT use, age, obesity and breast cancer risk

The breast cancer risks found in the WHI trial and the MWS study were independent of the age and the weight of the women, because the randomization process in the WHI trial led to a balanced distribution of women according to age and body mass index. In the MWS study, all relative risks were adjusted for eight characteristics of the women, including exact age and body mass index. Therefore, arguments rejecting or downplaying the results of these studies on the basis of differences between usual HRT users in France and women participating in the WHI trial or the MWS study are invalid.

Impact of the WHI and of MWS results on HRT use

As a final note, since publication of the WHI trial results in 2002, HRT use has started to fall in many countries, including France. For example, between the end of 2002 and the end of 2003, 28.3% of women in the Rhône-Alpes region ceased taking HRT (Gayet-Ageron et al., 2005). In the USA, the fall was particularly marked and it seems that the first signs of a subsequent decline in breast cancer incidence are already observable (Clarke et al., 2006; Ravdin et al., 2007).

Other aspects relevant to HRT and breast cancer are further covered in the Discussion, such as the role of the formulation and type of HRT used, and the French studies on HRT use and breast cancer.

2. Definition of exposure

The risk of breast and of ovarian cancer associated with HRT is related to current use of these medicines. Cancer risk decreases rapidly after cessation of HRT and falls to zero after a few years. Therefore, no lag-time between HRT use and breast or ovarian cancer occurrence was considered in this analysis.

3. Data used for RR estimates

Cohort studies other than the MWS (2003) that provided data on current HRT use for 4 or 5 years and more included a total of 178 920 women (Table B7.1). If a meta-analysis of risk associated with HRT was performed, because of the size of the MWS (1 084 110 women), the summary relative risks would be nearly equal to those found in this study. We therefore used estimates from the Million Women Study (2003), a large cohort study conducted in the UK that included 1 084 110 women aged 50–64 years, recruited between 1996 and 2001 and followed during an average of 2.6 years. Estimates from the WHI trials are not optimal as trial stopping rules were based on a combination of several endpoints. Also, the MWS was more representative of HRT use by women in Europe.

4. Data used for exposure prevalence

A national survey was conducted in France in 2003, as part of a survey covering Germany, the UK, France and Spain (Strothman & Schneider, 2003). This survey reported duration of HRT use for France that allowed estimation of proportions of French HRT users by duration of HRT use. For this survey, representative national samples of women 45–75 years of age were constituted through quota methods based on telephone directories. Data were collected through telephone interviews. Information on the total number of women contacted and on response rates was not reported. In France, the final sample included 2004 women aged 45–75 years, of whom 454 (23%) reported current HRT use.

Proportions of women taking E or E+P were derived from the ESPS-EPAS survey cited in the AFSSAPS report of 2005, according to which 17% of HRT users took E only and 83% took E+P. The ESPS-EPAS survey was conducted every four years

on a sample of French citizens registered in three main social-security offices. For HRT use, data were available for 1532 women 40 years old or older in 2000, and 1558 women 40 years old or older in 2002. This survey did not report duration of HRT use.

5. Calculation of AFs

Breast cancer

Table B7.3 provides details of AF calculations for breast cancer. Categories of duration of HRT use in the MWS study (2003) had a one-year difference from those of Strothman and Schneider (2003), but this difference was not likely to affect the AF estimates appreciably. The overall AF was 18.8% for women aged 45–75 years. In 2000, there were 28 288 breast cancer cases and 5958 deaths from breast cancer in French women aged 45–74 years (numbers and deaths from breast cancer at exactly 75 years old were not available). Thus in France, in the year 2000, 5313 breast cancer cases and 1119 breast cancer deaths could be attributed to HRT use. These figures represent 12.7% of breast cancer cases and 10.2% of breast cancer deaths in women of all ages.

Ovarian cancer

Table B7.4 provides details of AF calculations for ovarian cancer. Categories in the MWS (2003) had a one-year difference from those of Strothman and Schneider (2003), but this difference was not likely to affect the AF estimates appreciably. The overall AF was 3.5% for women aged 45–75 years, representing 101 ovarian cancer cases and 62 ovarian cancer deaths. In 2000, there were 4488 ovarian cancer cases and 3210 deaths from ovarian cancer. Thus in France, in the year 2000, according to the MWS data, HRT could have been the cause of 2.6% of ovarian cancer cases and 2.2% of ovarian cancer deaths in women of all ages.

6. Discussion

Comparison with estimates in the AFSSAPS report of 2005

The survey by Strothman and Schneider was conducted in 2003 and according to data on HRT use in the Rhône-Alpes region (Gayet-Ageron et al., 2005), it is unlikely that results from the WHI trial and the MWS study published in 2002 and 2003 had already led to cessation of HRT prescription in France. The survey by Strothman and Schneider sampled women 45 to 75 yeas old, and confirmed data showing that a non-negligible fraction of French women 65 years old and more were taking HRT, essentially for prevention of osteoporosis (Aubry and Guégen, 2002).

The AFSSAPS report of 2005 estimated an AF of 3–6% for women 40 to 65 years of age, such that an annual number of 650 to 1200 breast cancer cases in France in the years 2000–2002 would be due to HRT use (AFSSAPS 2005). Estimates made in the 2005 AFSSAPS report were based on rates of HRT use in women 40 to 64 years of age derived from various databases, one of them being the ESPS-EPAS survey we used ourselves to estimate numbers of women taking E or E+P. For relative risks of HRT use and breast cancer, the AFSSAPS looked at four different hypothetical risk scenarios for various forms of estrogens and progestogens, used alone or in combination, taking into account the duration of HRT use (i.e., <5 or ≥5 years). Relative risks taken from four studies (CGHFBC, 1997; Chlebowski et al., 2003; MWS, 2003; Fournier et al., 2005) were attributed to each hypothesis, but the relative risks used were chosen from different studies according to duration of use of HRT. Breast cancer numbers in France were estimated using data produced by the FRANCIM network of French cancer registries. The numbers of breast cancers attributable to HRT use were then calculated using a mathematical model applied to each risk hypothesis and whose inputs were, among other parameters, the chosen relative risks and the proportions of women taking the different types of HRT. The differences between our estimates and the AFSSAPS ones have four main origins:

(1) The RRs we used from the MWS (2003) are higher than those used in the AFSSAPS report. The following considerations support the use of higher RRs:

(i) Cohort studies in Nordic countries including a variety of HRT preparations provide support for the RRs from the MWS (Table B7.1).

(ii) In some models, the AFSSAPS report used

an RR of 1.24 from the intent-to-treat analysis of the WHI trial (Chlebowski et al., 2003). The intent-to-treat analysis was performed according to the number of women allocated to the intervention group, and the presence in the intervention group of women who did not take HRT decreased the RR found in this group. The RR of 1.49 found for women in the intervention group who actually took HRT was more appropriate for estimating attributable fractions.

(iii) In some models, the AFSSAPS report considered that E+micronized progesterone conveyed no increased risk of breast cancer.

(2) The AFSSAPS report considered women 40–64 years of age, while we considered women 45–75 years of age. The age range we considered was probably more representative of HRT use by French women because, as observed in many other countries, at least one report shows that a proportion of French women 65 years old and more were taking HRT, essentially for prevention of osteoporosis (Aubry and Guégen, 2002). Also, because it was a survey on a random sample of the population, the study of Strothmann and Schneider (2003) was probably more representative of the French female population, in spite of its relatively small size and limitations in the reporting of the survey methods used (e.g., the proportion of non-responders was not reported). The women in the MWS were younger (50–64 years at cohort inception) than in the Strothmann and Schneider survey (45–75 years), but the WHI trial has shown that risk of breast cancer associated with HRT after menopauses was independent of age and of the same magnitude in women 50–59, 60–69, and 70–79 years of age.

Formulation and route of administration of HRT

The HRT formulation used in the WHI trial for non-hysterectomized women was an association of a continuous combination of oral conjugated equine estrogens (CEE 0.625 mg/day) and a synthetic progestogen, medroxyprogesterone acetate (MPA 2.5 mg/day). The MWS mainly studied risk associated with estrogens combined with MPA, norethisterone or norgestrel. In Nordic countries, HRT incorporating testosterone derivatives is widely used. Hence, the trials on HRT reported to date (HERS II and WHI), the MWS study and cohort studies in Nordic countries and in the USA did not investigate all forms of HRT regimens, some of which are more commonly used in France (e.g., transdermal preparations, or natural progestogens in the form of micronized progesterone (E + micronized P)). For this reason, uncertainties remain on the real breast cancer risk associated with some HRT formulations (Modena et al., 2005), although the biological mechanisms of these formulations seem not very different from those of other forms of HRT (IARC 2007; Rochefort and Sureau, 2003). The possibility of a difference in breast cancer risk according to formulation and route of administration was stimulated by the French E3N cohort study which found in a first report that women currently using HRT containing micronized progesterone had a breast cancer risk of 0.9 (95% CI 0.7–1.2) that contrasted with a risk of 1.4 (95% CI 1.2–1.7) in women who were current users of other E+P formulations (Fournier et al., 2005). In a further report (Fournier et al., 2007), breast cancer risks were presented according to the type of progestogen used, but without considering the route of administration. The latter study was the first to show breast cancer risk according to various types of progestagen (e.g., progesterone, dydrogesterone, other progestagens) and has no equivalent in the literature.

Results of the E3N cohort study on E + micronized P conflict somewhat with those from the PEPI trial (Greendale et al., 2003) that found an increase in radiological breast density in women taking E + micronized P similar to the increase observed in women taking a continuous oral combination of conjugated equine estrogens (CEE 0.625 mg/day) and MPA (2.5 mg/day) – the formulation used in the WHI trial – or continuous conjugated equine estrogens (CEE 0.625 mg/day) and cyclic MPA (2.5 mg/day) on days 1–11. Radiological breast density is now known to be the main risk factor for breast cancer occurrence (Boyd et al., 2005) and one would expect that a specific HRT preparation leading to an increase in radiological breast density similar to that observed with other types of HRT would be associated with an equivalent increase in breast cancer risk.

The E3N study is the only study to date on specific transdermal HRT preparations, and these results need to be confirmed by other studies before validation of the conclusion that transdermal E +

micronized P does not convey a higher risk of breast cancer. This conclusion was also reached by the AFSSAPS in its last revision of the HRT issue in June 2006 (AFSSAPS, 2006). The best way to disentangle the issue of the HRT composition and formulation would be to have large studies organized to assess the health effects of HRT preparations that were not studied in the HERS II, WHI, MWS and Nordic cohort studies. The preferable way forward would be a randomized controlled trial of a transdermal HRT preparation containing E + micronized progesterone. In the absence of further confirmatory data on cancer risk associated with some HRT preparations, it is better to base public health thinking on the best available scientific evidence that has been repeatedly found in the WHI trial, the MWS and the Nordic cohort studies.

Studies on HRT use and breast cancer in France other than the E3N cohort study

Two studies in France compared breast cancer occurrence in women who were or who were not prescribed HRT (de Lignières et al., 2002; Chevallier et al., 2005; Espié et al., 2006). These two studies used designs that are unconventional in epidemiological research.

The first study included 3175 women who attended a large endocrinology outpatient clinic at least once between January 1975 and December 1987, and who were postmenopausal or 50 years old or more at some point during the period of inclusion (de Lignières et al., 2002). The mean duration between inclusion in the study group and the end of observation was 8.9 years (range: 1 to 24 years). Histories of HRT use and of breast cancer diagnosis were retrospectively reconstituted from medical files or from direct contact with the women. The denominators for numbers of woman-years of observation were calculated from first visit to the clinic if women were postmenopausal (this first visit could have taken place before 1975), or from the date of menopause if it occurred after January 1975. Women were not included if they had a diagnosis of breast cancer before potential inclusion in the study. Breast cancer occurrence was compared between women who used HRT and those who did not. After adjustment for age at menopause, year of birth and calendar period, the risk of breast cancer in ever-users of HRT was 1.03 (95% CI 0.61–1.75) for 5–9 years of use, and 1.15 (95% CI 0.64–2.05) for use for 10 years or more. Current HRT users had a relative risk of 0.83 (95% CI 0.51–1.83), and former users (use stopped in the four years before breast cancer diagnosis) had a relative risk of 1.42 (95% CI 0.76–2.44).

The second study, called the MISSION study, comprised two distinct phases: a historical phase estimating breast cancer risk according to past HRT use, and a prospective phase still in progress aiming at examining associations between HRT use and incidence of new breast cancer cases. The MISSION study included 6755 women who attended the practice of 825 volunteer gynaecologists between 5 January 2004 and 28 February 2005 (Chevallier et al., 2005; Espié et al., 2006). All women were postmenopausal at study inclusion. Using a standard random procedure, each gynaecologist had to sample eight women, four currently using or having used HRT within the last five years (the “treated group”) and four not using and not having used HRT within the last five years (the “untreated group”). Results published so far are those of the historical phase (Espié et al., 2006). All data came from medical records of women who attended gynaecologic private practices. Histologically-proven breast cancer cases were included in the analysis if they occurred after the menopause, and, in the treated group, if they had been diagnosed after the first dose of HRT. Mean HRT use during this phase was 7.9 years. According to medical records, over the entire period of retrospective gathering of data, i.e., from the first contact of women after menopause with their gynaecologist until study inclusion in 2004, 1.0% of women in the treated group and 6.2% of women in the untreated group had a breast cancer after menopause (i.e., the prevalent breast cancer cases). Standardized breast cancer incidence rates from 1 January 2003 until 31 December 2003, that is during the year before start of inclusion of women in the study, were calculated and age-adjusted taking the standard European population as reference. These age-adjusted incidence rates were then compared with age-specific incidence rates provided by the FRANCIM network of French cancer registries. The standardized incidence rate (SIR) of breast cancer in women in the “treated” group was 1.04 (95% CI 0.35–3.15), while the SIR in women of the “untreated” group was 2.50 (1.24–3.36).

The study by de Lignières et al. (2002) and the

MISSION study yielded results suggesting no increase in breast cancer risk with HRT use, regardless of current utilization or duration of utilization. This is in sharp contrast with the results from the US, UK, Nordic and French E3N prospective studies. In fact, these considerable differences in results proceed from the severe biases that may affect retrospective studies of the kind that were used in both studies. Biases possibly affecting the results from these two studies are:

(1) The two study designs resemble retrospective cohort studies, but neither of them provided information on data collection completeness, that is, up to what point medical records were accurate and up-to-date, or for how many women the disease status (breast cancer yes or no) had been assessed up to the end of the observation period. Cohort studies inevitably have subjects who are lost to follow-up (i.e., subjects included in the study for whom data on the main endpoint are missing). No loss to follow-up was reported by the two studies. This detail indicates that in both studies, the retrospective assessment of HRT use and of breast cancer occurrence did not include all women who were present at the beginning of the retrospective observation period, because in the meantime, a number of women no longer attended the gynaecology clinic or practice, for instance because of a breast cancer diagnosed in another medical facility that remained unknown to the gynaecologist. Such selection bias would work towards exclusion from the retrospective cohort of women more susceptible to develop a breast cancer. More specifically, for each study:

a) The study by de Lignières et al. (2002) did not report the number of women for whom the retrospective data collection did not extend until study termination on 1 December 1995. Retrospective data collection was also interrupted in case of death, but the investigators seem to have been ignorant of the cause of death. Hence, because of the absence of links with a complete population-based cancer registry, investigators may well have remained ignorant of a fraction of the women who developed a breast cancer and were diagnosed and treated elsewhere. Because of the relatively small number of breast cancers in this study (105 in total), retrieval of few missing breast cancer cases could have led to major changes in the results.

b) The MISSION study presents additional sources of bias linked to misclassification of exposure and of disease status, and to selection biases of women included in the study. Table B7.2 illustrates the sources of bias that may account for a large part of the considerably higher number of breast cancers found among “untreated” women than among “treated” women. The same misclassification and selection biases also affected the retrospective estimation of breast cancer incidence performed for the year 2003, before study inclusion. These biases in both exposure and disease assessment will also undermine the prospective part of the study, that is likely to yield results as biased as those from the retrospective study.

(2) Patients attending gynaecological clinics do not represent a natural cohort of the female population, or even of a specific segment of the female population, such as nurses or teachers. Women attend gynaecologists for a variety of reasons. In this respect, women to whom HRT was prescribed were therefore probably not comparable to women to whom HRT was not prescribed, and it is known that French women taking HRT have a different breast cancer risk profile to non-HRT users (Fournier et al., 2005, 2007).

a) The study by de Lignières et al. (2002) performed statistical adjustments for only three factors associated with breast cancer, and did not adjust for a number of other known important risk factors for breast cancer that could be unevenly distributed between HRT users and non-users (e.g., reproductive factors, body mass index, use of mammographic screening).

b) In the MISSION study, women who received HRT were younger, weighed less, were taller, had lower body mass index, were of higher socio-economic status, had slightly earlier menarche, had a late menopause less often, had less children, lower breastfeeding time, and fewer first-degree relatives with breast cancer than women who did not receive HRT. This imbalance in known breast

cancer risk factors may partly explain the results obtained by this study.

In conclusion, it is impossible to draw from these two studies any conclusion on the association between HRT use and breast cancer occurrence.

Reasons why breast cancer risk associated with HRT use in France should not be underestimated

Regardless of methodological issues, there are at least four good reasons why breast cancer risk associated with HRT use in France should not be underestimated:

(1) The proportion of women taking E+P combinations is higher in France than in the USA or the United Kingdom. In the WHI trial, of 100 women who took HRT in the past, 38% had taken E and 62% had taken E+P. In the MWS, these proportions were 34% and 66%, respectively. In the French E3N cohort, the proportions were 12% and 88% respectively. In the ESPS-EPAS survey cited in the AFSSAPS report of 2005, about 17% of women taking HRT took E only and 83% took E+P. Since E+P confers a higher breast cancer risk than E only, a greater proportion of breast cancers occurring in French women taking HRT can be attributed to HRT than in the USA or the United Kingdom.

(2) Even if one assumes that the combination of E + transdermal P (i.e., the "French HRT regimen") was associated with a lower or no increase in breast cancer risk, the fact remains that 83% of women using HRT in France did use HRT found by American, UK and Nordic studies to be associated with elevated breast cancer risk, and thus a part of the breast cancer diagnosed in French postmenopausal women is attributable to HRT use.

(3) As explained above, the results from the WHI trial and the MWS cohort were independent of body mass index by virtue of equal distribution of women's characteristics thanks to randomization in the WHI trial and to statistical adjustment for women's characteristics in the MWS study. But randomization and adjustment methods do not preclude that the effect of HRT on breast cancer risk could vary with body mass index. In the WHI trial, the MWS and the US cohort, the breast cancer risk associated with HRT increased substantially with decreasing body mass index (Chlebowski et al., 2003; Reeves et al., 2006; Schairer et al., 2000). Lean women have less endogenous production of estrogens than fatter women, and therefore may be more sensitive to exogenous estrogens. In 2003, 11% of adult French women were obese (see Section B5), while in 2002, 25% of British women were obese (Rennie and Jebb, 2005), and obesity levels in the USA are higher than in the United Kingdom (data from CDC Atlanta on www.cdc.gov). Hence, French women would be more sensitive to exogenous estrogens than British or US women, and the risks found in the WHI and MWS studies could well be underestimates for French women, assuming that all HRT formulations actually have about the same influence on breast cancer risk.

(4) Since 1980, a great variety of progestogen has been widely prescribed in France to premenopausal women to treating various premenopausal conditions as well as for contraception (Lowy and Weisz, 2005; Fournier et al., 2005b). The impact of this prescribing pattern on breast cancer risk was unknown until the E3N cohort study recently showed that use by French women 40–49 years old of progestogens for longer than 4.5 years was significantly associated with breast cancer risk (RR 1.44, 95% CI 1.03–2.00) (Fabre et al., 2007).

II. Oral contraceptives (OC)

In 2005, OC were classified as class 1 carcinogenic agents by the IARC (Cogliano et al., 2005). Current OC use entails a modest but real increase in breast cancer risk that disappears about 10 years after cessation of OC use. Reasons underlying this classification can be found at the url: http://monographs.iarc.fr/ENG/Meetings/91-contraceptives.pdf

1. Definition of exposure

Women 15 to 45 years old who are current users of oral contraceptives (OC). No lag-time was considered in the analysis.

Available data on OC use and cancer relate to first and second generations of OCs. There are not

yet any data on third-generation OCs.

2. Data used for RR estimates

We used data from the pooled study conducted by the Collaborative Group on Hormonal Factors in Breast Cancer (Oxford, UK). In an analysis of 53 297 women with breast cancer and 100 239 women without breast cancer from 54 epidemiological studies, the estimate of breast cancer risk among current users was 1.24 (95% CI 1.15–1.33) (Collaborative Group on Hormonal Factors in Breast Cancer, 1996).

3. Data used for exposure prevalence

In 2001, a national survey was conducted in France on a representative sample of women (Laveissière et al., 2003). Questionnaires were self-administered and sent by post to 5000 women aged 15–45 years old. Answers from 3609 women were received (response rate was 72%).

4. Calculation of AF

The prevalence of women taking OCs was derived from the French national survey (Table B7.5). AFs were computed for each age group, taking an RR of 1.24, and then summed. AFs were found of 7.8% for incidence and of 7.7% for mortality. In 2000, there were 5320 cases and 762 deaths from breast cancer among women 15–45 years of age. Thus in women aged 15–45 years in 2000, 414 incident breast cancer cases and 59 breast cancer deaths could be attributed to current OC use. These figures represent 1.0% of breast cancer cases and 0.5% of breast cancer deaths in women of all ages.

5. Discussion

OCs have been classified as a Group 1 carcinogenic agent by the IARC (Cogliano et al., 2005) and current OC use entails a modest but real increase in breast cancer risk, that disappears in the years following cessation of OC use. Although current OC use is the cause of a minority of breast cancers, current and past OC use has the following major benefits:

(1) Decrease in ovarian and endometrial cancers. In this respect alone, considering the overall cancer burden in women, the overall balance for OC use is positive, with more benefit than risk.

(2) Decrease of health hazards associated with unwanted and rapidly successive pregnancies.

(3) Major decrease in extra-uterine pregnancies.

(4) Decrease in salpingitis, benign functional ovarian cysts and benign breast diseases

(5) OC use increases medical contacts, resulting in better compliance with cervical cancer screening

References

AFSSAPS. Agence Française de Sécurité Sanitaire des Produits de santé. Traitements hormonaux substitutifs de la ménopause, Rapport d'orientation, 11 Mai 2004.

AFSSAPS. Agence Française de Sécurité Sanitaire des Produits de santé. Traitement hormonal substitutif de la ménopause. Septembre 2005.

AFSSAPS. Agence Française de Sécurité Sanitaire des Produits de santé. Mise au point: Le traitement hormonal de la ménopause. Point d'étape juin 2006.

Anderson GL, Limacher M, Assaf AR, et al. for the Women's Health Initiative Steering Committee. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: The Women's Health Initiative randomized controlled trial. JAMA 2004;291:1701–1712.

Aubry C, Guégen R. Tableau de bord de la santé en Haute-Marne, années 1996 à 2000. Centre de Médecine Préventive de Nancy-Vandoeuvre, Observatoire du Centre de Médecine Préventive de Vandoeuvre, 2002.

Bakken K, Alsaker E, Eggen AE, Lund E. Hormone replacement therapy and incidence of hormone-dependent cancers in the Norwegian Women and Cancer study. Int J Cancer 2004;112:130–134

Boyd MF, Rommens JM, Vogt K, et al. Mammographic breast density as an intermediate phenotype for breast cancer. Lancet Oncol 2005;6:798–808

CGHFBC. Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and hormone replacement therapy: Collaborative reanalysis of data from 51 epidemiological studies of 52,705 women with breast cancer and 108,411 women without breast cancer. Lancet 1997;350:1047–1059.

Chevallier T, Daurès JP, Micheletti MC, Reginster JY. Méthodologie de l'enquête mission (ménopause, risque de cancer du sein, morbidité et prévalence). J Gynecol Obstet Biol Reprod 2005; 34 (cahier 1):658–665.

Chlebowski RT, Hendrix SL, Langer RD, et al. Influence of estrogen plus progestogen on breast cancer

and mammography in healthy postmenopausal women: The Women's Health Initiative Randomized Trial. JAMA 2003;289:3243–3253

Clarke CA, Glaser SL, Uratsu CS, et al. Recent declines in hormone replacement therapy utilization and breast cancer incidence: clinical and population-based evidence. J Clin Oncol 2006;33:e49–e50.

Cogliano V, Grosse Y, Baan R, et al for the WHO International Agency for Research on Cancer. Carcinogenicity of combined oestrogen-progestagen contraceptives and menopausal treatment. Lancet Oncology 2005;6:552–553.

Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and hormonal contraceptives: collaborative reanalysis of individual data on 53 297 women with breast cancer and 100 239 women without breast cancer from 54 epidemiological studies. Collaborative Group on Hormonal Factors in Breast Cancer. Lancet 1996;347:1713–1727.

Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and hormone replacement therapy: Collaborative reanalysis of data from 51 epidemiological studies of 52,705 women with breast cancer and 108,411 women without breast cancer. Lancet 1997;350:1047–1059.

De Lignières B, de Vathaire F, Fournier S, et al. Combined hormone replacement therapy and risk of breast cancer in a French cohort study of 3175 women. Climacteric 2002;5:332–340.

Espié M, Mares P, De Reilhac P, et al.. Breast cancer in postmenopausal women with and without hormone replacement therapy: Preliminary results of the Mission study. Gynecological Endocrinology 2006;22:423–431.

Ewertz M, Mellemkjaer L, Poulsen AH, et al. Hormone use for menopausal symptoms and risk of breast cancer. A Danish cohort study. Br. J. Cancer, 2005;92:1293–1297

Fabre A, Fournier A, Mesrine S, et al. Oral progestagens before menopause and breast cancer risk. Br J Cancer 2007; 96: 841–844.

Fournier A, Berrino F, Riboli E, et al. Breast cancer risk in relation to different types of hormone replacement therapy in the E3N-EPIC cohort. Int J Cancer 2005;114:448–454.

Fournier A, Berrino F, Riboli E, et al. Re: Breast cancer in HRT use (Letter to the Editor). Int. J. Cancer 2005;116:999.

Fournier A, Berrino F, Clavel-Chapelon F. Unequal risks for breast cancer associated with different hormone replacement therapies: results from the E3N cohort study. Breast Cancer Res Treat. 2007 DOI 10.1007/s10549-007-9523-x

Gayet-Ageron A, Amamra N, Ringa V, et al. Estimated numbers of postmenopausal women treated by hormone replacement therapy in France. Maturitas 2005;52:296–305

Greendale GA, Reboussin BA, Wasilaukas C, et al. Postmenopausal hormone replacement therapy and change in mammography density. J Natl Cancer Inst 2003;95:30–37.

Hulley S, Furberg C, Barrett-Connor E, et al. Noncardiovascular disease outcomes during 6.8 years of hormone replacement therapy: Heart and Estrogen/progestogen Replacement Study follow-up (HERS II). JAMA 2002;288:58–66

Jernström H, Bendahl PO, Lidfeldt J, et al. A prospective study of different types of hormone replacement therapy use and the risk of subsequent breast cancer: The Women's Health in the Lund area (WHILA) study (Sweden). Cancer Causes Control 2003;14:673–680.

International Agency for Research on Cancer. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 91, Oestrogen-progestogen replacement therapy and combined oral contraceptives, 2007 (in press).

Laveissière MN, Pelissier C, Le MG. La contraception orale en France en 2001 : résultats d'une enquête par sondage portant sur 3609 femmes âgées de 15 à 45 ans. Gynécologie Obstétrique Fertilité 2003;31:220–229.

Lopes P. Que penser des résultats de la Women's Health Initiative (WHI) et de la Million Women Study (MWS) qui remettent en question l'intérêt du traitement hormonal de la ménopause ? J Gynecol Obstet Biol Reprod 2003;6:500–502.

Lowy I, Weisz G. French hormones: progestogens and therapeutic variation in France. Social Sci Med 2005;60:2609–2622

Million Women Study Collaborators. Breast cancer and hormone-replacement therapy in the Million Women Study. Lancet 2003;362:419–427.

Million Women Study Collaborators. Ovarian cancer and hormone-replacement therapy in the Million Women Study. Lancet 2007;369:1703–1710.

Modena MG, Sismondi P, Mueck AO, et al. New evidence regarding hormone replacement therapies is urgently required, transdermal postmenopausal hormone replacement therapy differs from oral hormone replacement therapy in risks and benefits. Maturitas 2005;52:1–10.

Olsson HL, Ingvar C, Bladstrom A. Hormone replacement therapy containing progestogens and given continuously increases breast carcinoma risk in Sweden. Cancer 2003;97:1387–1392.

Persson, I., Weiderpass, E., Bergkvist, L., et al. (1999)

Risks of breast and endometrial cancer after estrogen and estrogen–progestogen replacement. Cancer Causes Control 10, 253–260

Ravdin PM, Cronin KA, Howlader N, et al. The decrease in breast cancer incidence in 2003 in the United States. New Engl J Med 2007;356:1670–1674.

Reeves GK, Beral V, Green J, et al. Hormonal therapy for menopause and breast cancer risk by histological type: a cohort study and meta-analysis. Lancet Oncol 2006;7:910–918.

Rennie KL, Jebb SA. Prevalence of obesity in Great Britain. Obes Rev 2005;6:11–12.

Rochefort H, Sureau C .Les traitements hormonaux substitutifs (TSH) de la ménopause: évolution récente du rapport bénéfices/risques Bulletin de l'Académie Nationale de Médecine, séance du 2/12/2003, 187, 1707–1711, on the web site: www.academie-medecine.fr

Rossouw JE, Anderson GL, Prentice RL et al. for the Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestogen in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. JAMA 2002; 288: 321–333.

Schairer C, Lubin J, Troisi R, et al.Menopausal estrogen and estrogen–progestogen replacement therapy and breast cancer risk. JAMA 2000;283:485–491

Shapiro S. The Million Women Study: potential biases do not allow uncritical acceptance of the data. Climacteric 2004;7:3–7.

Stahlberg C, Pedersen AT, Lynge E, et al. Increased risk of breast cancer following different regimens of hormone replacement therapy frequently used in Europe. Int J Cancer 2004;109:721–727.

Strothmann A, Schneider HPG. Hormone therapy: The European women's perspective. Climateric 2003;6:337–346.

Tjønneland A, Christensen J, Thomsen BL, et al. Hormone replacement therapy in relation to breast carcinoma incidence rate ratios: A prospective Danish cohort study. Cancer 2004;100:2328–2337.

van der Mooren MJ, Kenemans P. The Million Women Study: a licence to kill other investigations? Eur J Obstet Gynecol Reprod Biol 2004;113:3–5.

Whitehead M, Farmer R. The million women study: a critique. Endocrine 2004;24:187–193.

Table B7.1 - Hormone replacement therapy and risk of breast cancer in cohort studies

Reference	Country	Cohort size	Average follow-up in years	Type of HT use and duration	Relative risk* users vs. non users	95% Confidence interval	Number of breast cancers among users
Persson 1999	Sweden	10 472	6	E+P, ≥ 6 years†	1.72	1.1-2.6	44
Schairer 2000	USA	46 355	15	E+P, ≥ 5 years	1.50	1.12-1.96	19
Olsson 2003	Sweden	29 508	10	E+P sequential, > 4 years	1.44	0.67-3.08	NR
				E+P continuous, ≥ 4 years	3.13	1.70-5.75	NR
Jernström 2003	Sweden	6 586	4.1	E+P continuous, ≥ 5 years	3.2	1.4-7.2	NR
Million Women Study 2003	UK	1 084 110	2.6	Any	1.66	1.60-1.72	3 202
				Oral E+P	2.00	1.91-2.09	1 934
				Oral E+P continuous, ≥ 5 yrs	2.40	2.15-2.67	388
				Oral E+P sequential, > 5 yrs	2.12	1.95-2.30	778
Tjonneland 2004	Denmark	29 875	4.8	Current	2.22	1.80-2.75	227
Stahlberg 2004	Denmark	19 898	6	Any	2.42	1.81-3.26	103
Bakken 2004	Norway	31 451	NR	E+P sequential, ≥ 5 years	2.2	1.3-3.8	19
				E+P continuous, > 5 years	3.2	2.2-4.6	37
Erwetz 2005	Denmark	73 380	10	Any	1.61	1.38-1.88	222
Fournier 2005a§	France	54 548	5.8	Any	1.2	1.1-1.4	NR
				Oral E+P	1.5‡	1.1-1.9	80
				Oral E+P, > 4 years	1.9‡	1.2-3.2	17

E: Estrogens; P: progestins; NR: not reported

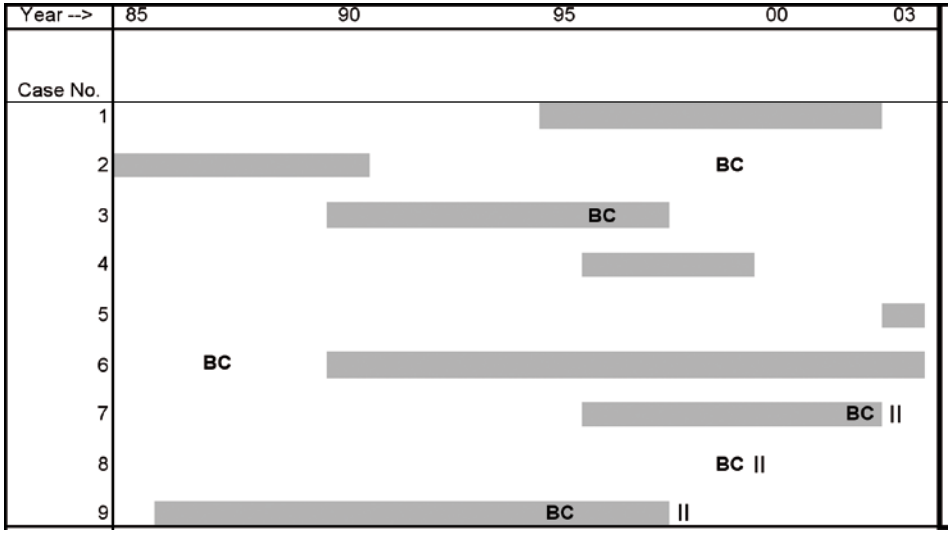
* Adjusted on age, BMI, follow-up time, and age at menopause

† RR may be underestimated because 9 women with breast cancer had stopped HT more than one year before diagnosis

‡ No difference between sequential and continuous use

§ Results in Fournier et al, 2005a were more comparable to other studies in Table than results from Fournier et al, 2007

Table B7.2 – Examples of sources of misclassification of exposure or of disease status, and of selection bias in the MISSION study (Chevallier et al., 2005; Espié et al., 2006). Thick grey lines represent years of HRT use, "BC" denotes breast cancer diagnosis and "II"denotes women no longer attending the gynaecology practice where the MISSION study was conducted



	Status for the MISSION study			Real status	
Case No.	Included in the study in 2004	Considered as "Treated" with HRT	Considered as a breast cancer case	Treated with HRT	BC case
1	YES	YES	NO	YES	NO
2	YES	**NO**	YES	**YES**	YES
3	YES	**NO**	YES	**YES**	YES
4	YES	**YES**	NO	**NO**	NO
5	YES	**YES**	NO	**NO**	NO
6	YES	YES	**NO**	YES	**YES**
7	NO	-	-	**YES**	**YES**
8	NO	-	-	**NO**	**YES**
9	NO	-	-	**YES**	**YES**

Comments to the Table: Definition of treated women in the MISSION study was using or having used HRT within the last 5 years, and of untreated women was not using and not having used HRT within the last 5 years. Breast cancers in the treated group were counted only when they had been diagnosed after the first dose of HRT. The three columns "Status for the MISSION study" relates to the coding practice of retrospective observations according to MISSION definitions. The two columns "Real status" refer to the true status of women in 2004 regarding their real history of HRT use and breast cancer occurrence that should have been known by investigators if the cohort had been complete (i.e., full follow-up of all women that should have been included in the cohort starting from a pre-defined year) and if definitions were in agreement with the known association patterns between HRT use and breast cancer.

The observation period in Table B7.2 starts in 1985, but the MISSION provided no directive about the earliest year from which the retrospective assessment of HRT use or of breast cancer occurrence until 2004 was to be done.

Case 1 corresponds to the definition of women belonging to the "treated group".

Case 2+3 woman was actually treated and was diagnosed with a breast cancer when taking HRT, but according to definitions used, she was considered as "untreated".

In Case 4, use of HRT for less than 5 years before inclusion in the study is considered as "treated", when impact of HRT on breast cancer decreases rapidly after treatment cessation. This resulted in increasing the number of women in the "treated group" that were unlikely to develop a breast cancer because of HRT use. In case 5, the women was considered as "treated" when she took HRT for less than one year, a duration unlikely to increase breast cancer risk.

In case 6, breast cancer diagnosed before HRT use is not counted, what artificially decreased the numerator in the "treated group".

Cases 7, 8 and 9 are women with BC and various exposures to HRT before 2003 that did not attend gynaecological practice in 2004. These women were thus not included in the study and thus contributed to a strong selection bias resulting in an "incomplete cohort".

Table B7.3 – Calculation of AFs for breast cancer and current use of HRT, according to time since first use

	% of women 45–75 taking HRT† (1)	% E or E+P (2) ‡	% of women 45–75 = (1) x (2)	RR of breast cancer §	AF
Estrogen (E) only					
Current use and use during less than 1 year	0.6%	17%	0.11%	1.00	0.0%
Current use and use during 1 to 5 years*	10.1%	17%	1.72%	1.25	0.4%
Current use and use during 6 to 10 years*	5.7%	17%	0.97%	1.32	0.3%
Current use and use during 10 years or more*	6.2%	17%	1.05%	1.37	0.4%
Total for E only					1.1%
Estrogen and progesterone (E+P)					
Current use and use during less than 1 year	0.6%	83%	0.51%	1.45	0.2%
Current use and use during 1 to 5 years*	10.1%	83%	8.40%	1.74	5.9%
Current use and use during 6 to 10 years*	5.7%	83%	4.76%	2.17	5.3%
Current use and use during 10 years or more*	6.2%	83%	5.13%	2.31	6.3%
Total for E+P					17.7%
Total for E and E+P					**18.8%**

* Categories of HRT use duration in the MWS (2003) had one-year difference with categories in Strothmann and Schneider (2003)

† % of women 45–75 taking HRT adapted from Strothmann and Schneider (2003)

‡ % taking E or E+P from ESPS-EAPS (AFSSAPS, 2005)

§ RR of breast cancer from MWS (2003)

Table B7.4 – Calculation of AFs for ovarian cancer and current use of HRT

	% of women 45–75 taking HRT† (1)	% E or E+P (2)	% of women 45–75 = (1) x (2)	RR of ovarian cancer	AF
Estrogen (E) only					
Current and <5 year	10.7%	17%	1.83%	1	0.0%
Current and ≥5 years*	11.9%	17%	2.03%	1.53	1.1%
Total for E only					1.1%
Estrogen and progesterone (E+P)					
Current and <5 year	10.7%	83%	8.91%	1.09	0.8%
Current and ≥5 years*	11.9%	83%	9.89%	1.17	1.7%
Total for E+P					2.4%
Total for E and E+P					**3.5%**

*Categories in the MWS (2003) had one-year difference from categories in Strothmann and Schneider (2003)

† % of women 45–75 taking HRT adapted from Strothmann and Schneider (2003). % taking E or E+P from ESPS-EAPS (AFSSAPS, 2005). RR of breast cancer from the MWS (2003)

Table B7.5 - Prevalence of current OC use in women 15–45 years old in France and attributable numbers of breast cancer (BC) cases and deaths

Age	% Current OC use	AF*	All breast cancer cases	All breast cancer deaths	No. breast cancer cases attributable to OC use	No. breast cancer deaths attributable to OC use
15–19	50%	10.7%	3	0	0	0
20–24	69%	14.2%	19	1	3	0
25–29	54%	11.5%	167	11	19	1
30–34	45%	9.7%	598	70	58	7
35–39	41%	9.0%	1562	251	140	22
40–44	29%	6.5%	2971	429	193	28
		BCs 15–44	5320	762	414	59
		%			7.8%	7.7%
		All BCs	41845	10950		
		% All BCs			1.0%	0.5%
		% All cancers			0.4%	0.1%

*Calculated taking an RR of 1.24

Section B8: Ultraviolet light

I. Sun exposure

1. Definition of exposure

Sun exposure is the main environmental cause of cutaneous melanoma, basal-cell carcinoma (BCC) and squamous-cell carcinoma (SCC) (IARC, 1992). This section focuses on cutaneous melanoma, which represents about 5% of all skin cancers, and is the most deadly form.

2. Data used for estimation of RR for cutaneous melanoma

No RR estimates were used (see below).

3. Data used for exposure prevalence.

No estimates of exposure were used (see below).

4.Calculation of the attributable fraction (AF)

It is difficult to satisfactorily quantify sun exposure, as many variables are involved, such as the total duration of sun exposure, sunbathing habits, sun protections used, and sun exposure during childhood, adolescence and adult life, all of which are known to have different effects on melanoma risk.

Consequently, use of Levin's method, with selection of some sun exposure indicators, would underestimate the AF of sun exposure for melanoma. The best alternative approach is to evaluate the proportion of cutaneous melanoma due to sun exposure by comparing the observed incidence of melanoma with estimates of incidence in the absence of sun exposure. This was done by Armstrong and Kricker (1993), who examined the difference in melanoma incidence between Australian-born and immigrant populations in Australia, which led to an estimate that 68% of all melanomas were attributable to sun exposure, irrespective of the time during life or type of sun exposure.

Taking an AF of 68% of melanoma associated with sun exposure, we can estimate that for France in the year 2000:

Incidence:	2085 melanoma in men and 2832 in women **1.3%** of all cancers in men and **2.4%** in women
Mortality:	480 deaths from melanoma in men and 437 in women **0.6%** of all cancer deaths in men and **0.8%** in women

II. Use of sunscreens containing 5-methoxypsoralen (5-MOP)

1. Definition of exposure

Psoralens are potent photocarcinogens and tanning occurs faster when these compounds are added to a skin lotion or taken orally. The association of 8-methoxypsoralen (8-MOP) and ultraviolet (UV) A has been classified as a Group 1 carcinogen (IARC, 1980, 1987). 5-Methoxypsoralen (5-MOP) is classified as a Group 2A carcinogen in the absence of ultraviolet A (IARC, 1986, 1987). In the presence of UVA, 5-MOP is a potent photocarcinogen (reviewed by Autier et al.,

1997). Sunscreen products containing 5-MOP are intended for use during exposure to sunlight (which contains large amounts of UVA) and can therefore be considered as a Group 1 carcinogen. In the 1980s, a French company added 5-MOP to sunscreens that were commercialized in France, Belgium and Greece, until 1995, when the EC put a ban on the use of these products by the general public (Autier et al., 1997; IARC, 2001).

2. Data used for RR estimation

RR = 2.28 for cutaneous melanoma in relation to ever having used 5-MOP sunscreens (from Autier et al., 1995).

3. Data used for exposure prevalence

In 1992, 8.3% of French adults ≥ 18 years old ever used 5-MOP sunscreens (from Autier et al., 1995).

4. Calculation of the AF

With 8.3% prevalence and a risk of 2.28, we estimate the AF associated with use of 5-MOP sunscreen to be 9.6%.

For France in 2000, this would represent 296 new cases of melanoma for men and 401 for women, and 68 deaths from melanoma for men and 62 deaths for women.

III. Discussion

There has been a sustained increase in incidence of cutaneous melanoma in France (5.9% per year in men from 1980 until 2000, and 4.3% per year in women; Remontet et al., 2002, 2003), and there is at present no sign of these trends levelling off.

The data we used for psoralen sunscreen use are not overestimated: one survey in 1989 among French adolescents 13–14 years old in the south of France reported that 50.0% of girls and 22.2% of boys occasionally or regularly used psoralen sunscreens to promote tanning (Grob et al., 1993). The risk associated with 5-MOP sunscreens will disappear with time, as these products are no longer publicly available.

SCC and BCC were not considered in this report, because reliable data on their incidence in France do not exist. In any case, SCC and BCC rarely evolve into invasive disease that may be fatal (invasive SCC or BCC often appear in immunocompromised people), and therefore the incidence of SCC and BCC is not recorded by most cancer registries. Nonetheless, the incidence of these two types of tumour is steadily increasing in most white-skinned populations, and because of their number, SCC and BCC have a considerable impact on health expenditure. Based on data on SCC and BCC gathered by the cancer registry of Doubs, an estimate for France made by H. Sancho-Garnier of the University of Montpellier (personal communication) foresees around 42 000 annual cases of SCC and BCC among French males, and 23 000 cases among French females. Most of these SCC cases will occur in the elderly and be due to a lifetime of chronic sun exposure (e.g., farmers, construction and road workers), and most BCC will be due to both chronic and intermittent sun exposure (e.g., sun exposure during holidays).

References

Armstrong BK, Kricker A. How much melanoma is caused by sun exposure? Melanoma Res. 1993;3:395–401.

Autier P, Doré JF, Schifflers E, et al. Melanoma and use of sunscreens: an EORTC case-control study in Germany, Belgium and France. The EORTC Melanoma Cooperative Group. Int J Cancer 1995;61:749–755.

Autier P, Doré JF, Cesarini JP, Boyle P. Should subjects who used psoralen suntan activators be screened for melanoma? Ann Oncol 1997;8:435–437.

Grob JJ, Guglielma C, Gouvernet J, et al. Study of sunbathing habits in children and adolescents: Application of the prevention of melanoma. Dermatology 1993;186:94–98.

International Agency for Research on Cancer. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Vol. 24, Some Pharmaceutical Drugs, Lyon, IARC, 1980.

International Agency for Research on Cancer. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Vol. 40. Some Naturally Occurring and Synthetic Food Components, Furocoumarins and Ultraviolet Radiation. Lyon, IARC, 1986.

International Agency for Research on Cancer. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Vol. 55. Solar and Ultraviolet Radiation. Lyon,

IARC, 1992.

International Agency for Research on Cancer. IARC Handbooks of Cancer Prevention, Vol. 5, Sunscreens. Lyon, IARC, 2001.

Remontet A, Buemi M, Velten, Jougla E, Estève J. Évolution de l'incidence et de la mortalité par cancer en France de 1978 à 2000. Rapport FRANCIM, Hôpitaux de Lyon, INSERM, InVS, 2002.

Remontet L, Esteve J, Bouvier AM, et al. Cancer incidence and mortality in France over the period 1978-2000. Rev Epidemiol Santé Publique. 2003;51:3-30.

Section B9: Reproductive factors

1. Definition of exposure

Reproductive factors include characteristics specifically related to a woman's history of giving birth, including age at menarche, number of births (parity), age at first birth, lactation (breastfeeding) and age at menopause. Each of these factors is associated with important changes in circulating estrogens and progesterone. Many publications have documented the importance of reproductive factors in a woman's risk of developing a cancer of the breast, ovary, endometrium, cervix or colon during her lifetime (e.g., Pathak et al., 2000; Pike et al., 1983, 1993). Cancer risk associated with each reproductive factor tends to increase or decrease incrementally throughout the range of the variable, so that there is no single low- or high-risk group. Also, reproductive factors are not independent; for instance, breastfeeding can only be considered in parous women. Therefore, disentangling specific effects of reproductive factors on cancer risks is difficult.

We found only very few published estimates of numbers of breast and ovarian cancers attributable to temporal changes in reproductive factors. Madigan et al. (1995) examined the number of breast cancers in the USA attributable to age at first birth, taking as the alternative scenario all women being parous and having their first child before 20 years of age. The attributable fraction was 29.5%, but the scenario chosen by these authors is not realistic: nowadays women tend to have their children after the termination of their studies (Bac et al., 2005), and there will always be a substantial proportion of women unable to give birth. Other similar types of scenario are even less realistic. For instance, one could calculate changes in cancer burden to be expected if all parous women alive in 2000 had had three children, but this would be pointless, as having one or more children is not motivated by a desire to decrease one's chance of developing breast or ovarian cancer.

In view of these difficulties, we adopted an original approach for assessing attributable risks associated with reproductive factors. We considered the difference in reproductive history of women alive in 2000 and of women alive in 1980. Reproductive history of women alive in 2000 or 1980 could be reconstructed thanks to the availability of data on parity of women according to five-year birth cohorts since 1902. The comparison year of 1980 was chosen because historical data on reproductive factors are not known for women born before 1902. The scenario we choose, looking at changes in reproductive factors between two years 20 years apart is a realistic approach as it corresponds to what actually happened in the French population.

In this report, we considered nulliparity, number of children, age at first birth and duration of breastfeeding. Unfortunately, for the last two factors, no data by birth cohort exist and we adopted other ways for estimating their prevalence in women alive in 2000 and 1980 (see below).

Risks associated with reproductive factors were assessed for breast (all four factors) and ovarian cancer (only the number of children). We did not consider reproductive factors for cancer of the corpus uteri and of the colon, as available data are fragmentary and sometimes contradictory. Reproductive factors for cervical cancer are now considered as surrogates for HPV infection, that is addressed in Section B3. Age at menarche and age at menopauses were not considered as we found no data on changes in these two factors between 1980 and 2000, though there are indications that since the 1980s, changes in these two factors were marginal (de la Rochebrochard, 2000 for age at menarche).

2. Data used for RR estimates

(1) In nulliparous women, relative risk of breast cancer is 1.36 (36% increase) as compared to parous women having one or more children (Layde et al., 1989; Ursin et al., 1994).

(2) There is only a statistically non-significant change in breast cancer risk between nulliparous women and women with only one child. After the first child, the risk of breast cancer decreases by 7% for each additional child (CGHFBC, 2002).

(3) In parous and nulliparous women, the risk of ovarian cancer decreases by 13% for each additional child (Harvard Report on Cancer Prevention, 1996).

(4) The RR for breast cancer is 1.67 in women whose first birth occurred at 30 years of age or older compared with first birth before 30 years of age (Layde et al., 1989; Ursin et al., 1994).

(5) Breast cancer risk decreases by 4.3% for each period of 12 months of breastfeeding (CGHFBC, 2002)

3. Data used for exposure prevalence

(1) For the prevalence of **nulliparous women,** we took data from the INED (Toulemon 2001, 2003; Toulemon and Mazuy, 2001) showing a considerable decrease in nulliparous women during the first half of the 20th century, followed by stabilization (Figure B9.1). Since the end of the Second World War, the proportion of high multiparous women has declined and the current persistent trend is towards stabilization at around two children per parous woman.

Data on the proportion of nulliparous women were available for five-year period birth cohorts since 1902. For instance, 22.8% of women born between 1902 and 1907 remained nulliparous during their lifetime, compared with 9.77% of women born between 1947 and 1952. Therefore, for each five-year age group in 1980 and 2000, we could calculate the number of nulliparous women among women who were 38 years old or older in 1980 and in 2000. For instance, the number of nulliparous women among women aged 38–42 years in 1980 was derived by multiplying the proportion of nulliparous women in the birth cohort 1938–1942 by the total number of women 38–42 years of age in 1980. The number of nulliparous women 38–42 years of age in 2000 was derived by multiplying the proportion of nulliparous women in the birth cohort 1958–1962 by the total number of women 38–42 years of age in 2000. We took women 38 years old or older at first birth as the lowest age limit for the estimation of parity as first birth after this age is not common.

These calculations showed that in 1980, 16.2% of women 38 years of age or older were nulliparous, versus 11.9% in 2000.

(2) For **fertility**, we calculated the mean number of children born to parous women alive in 1980 and 2000 using INED data on proportions of women who had zero, one, two, three and four or more children per five-year birth cohort since 1902. For instance, women born between 1902 and 1907 were between 73 and 78 years old in 1980, and between 93 and 97 year old in 2000. Figure B9.1 shows that the proportions of women born between 1902 and 1907 who gave birth to zero, one, two, three and four or more children during their lifetime were 22.8%, 23.9%, 21.6%, 12.8% and 18.8%, respectively. For women born between 1947 and 1952, these proportions were 9.8%, 20.0%, 38.4%, 20.3% and 11.6%, respectively. Computations were done in five steps:

(i) We subtracted from each five-year age group in 1980 and 2000 the number of nulliparous women obtained in the computations on nulliparity described above, which yielded the number of parous women 38 years old and older for each five-year age group in 1980 and 2000.

(ii) For each five-year birth cohort, we calculated the mean number of children among parous women using the formula:

$$[b+2c+3d+4.5e]/(100-a)$$

where *a, b, c, d, e* are the proportions of women with 0, 1, 2, 3, and ≥4 children in each five-year birth cohort, and $a+b+c+d+e = 100\%$. Because we had no details on the number of women with 4, 5, 6 etc… children for women who had four children or more, we used a parity factor of 4.5 instead of 4.0, to avoid too great an underestimation of the mean number of children.

(iii) For each five-year age group of parous women in 1980 and 2000, we applied the mean number of children per five-year birth cohort found

in (ii), which yielded the total number of children born to parous women alive in 1980 or in 2000.

(iv) For calculation of the AF for breast cancer, we divided the total number of children born to parous women in 1980 or in 2000 by the respective total number of parous women in 1980 and 2000, which yielded the mean number of children per parous woman in 1980 and 2000.

(v) For calculation of the AF for ovarian cancer, we divided the total number of children born to parous women in 1980 or in 2000 by the respective total number of women in 1980 and 2000, which yielded the mean number of children per woman in 1980 and 2000.

Figure B9.2 summarizes the fertility data for all French women (v) and for French parous women (iv). The mean number of children per woman and the mean number per parous woman tended to diverge as the date of the mother's birth approached 1902, as the proportions of nulliparous women were steadily higher with increasing age (Figure B9.1). Peak fertility was observed for women born between 1927 and 1937, i.e., those who were in reproductive age from the late 1940s to the early 1960s, corresponding to the baby-boom period. Fertility reverted to an average of two children per woman among women born after 1947 and has remained fairly stable since then.

Computations yielded an average number of 2.61 children per parous woman in 1980 and of 2.47 in 2000. Average numbers of children per women were 2.19 in 1980 and 2.17 in 2000. Women with higher fertility during the baby-boom period were proportionally more numerous in 1980 than in 2000, which explains the greater average number of children among parous women in 1980. But there were proportionally more nulliparous women in 1980 than in 2000, which explains the quite similar fertility rates in 1980 and 2000.

(3) Data on **age at first birth** were extracted from Graph 2 of Toulemon (2003). These INED data were corrected for proportions of nulliparous women in successive generations (Figure B9.3). Data were not available by birth cohort, but only as proportions by generation. According to the INED, data on childbirth during a specific year correspond to women born on average 28 years earlier (the "generation"). The earliest year with available data on this factor was 1970 and thus concerned the generation of 1942. Women in the year 2000 corresponded to the generation of 1972, and women in year 1980 corresponded to the generation of 1952. From Figure B9.3, the proportions of women who gave birth after 29 years of age were 25% in 1952 and 41% in 1972.

(4) For **breastfeeding,** we adopted the following steps:

(i) We used the proportion of women who ever breastfed provided by the INSERM U149, that concerned the years 1972, 1976, 1981, 1995, 1998 and 2003 (Blondel et al., 1997, 2001). The proportions of women who breastfed their children were 31.7% in 1972 and 56.5% in 2003. We extrapolated to the years between 1972 and 2003 using simple linear regression.

(ii) According to a survey performed by the Institut des Mamans (supported by La Leche League France[2]), the mean duration of breastfeeding in early 2000 was four months. We assumed that the duration was the same in 1985.

(iii) For periods before 1970, we used data from historical reports (Rollet, 2005) and one survey done in the Departments of Seine and Seine-et-Oise in 1952 (Lesné et al., 1953). In 1949, 57% of women breastfed newborns. That proportion fell to 38% in 1951 and to 32% in 1952. We considered that in 1955, 30% of mothers breastfed their child up to the third month after delivery.

(iv) The average duration (in months) of breastfeeding per woman was estimated for the different points in time for which we had data on the percentage of women who breastfed their newborn and estimates of the number of months of breastfeeding.

Figure B9.4 displays estimates of the average duration of breastfeeding in France, taking into account fertility rates in specific age groups. During

[2] La Leche League France on www.LLLfrance.org, and www.santeallaitementmaternel.com

the Second World War, breastfeeding was common; after the war, it declined sharply, reaching a minimum level in the 1950s and 1960s. In the past decade, there has been a modest revival in breastfeeding.

As for age at first birth, we considered the generations born in 1952 and 1972. From Figure B9.4, we derived that average numbers of months of breastfeeding for all children were 3.4 months in the 1952 generation and 4.2 months in the 1972 generation.

4. Calculation of AF

The data used in calculation of AFs are summarized in Table B9.1. We first calculated AFs for 1980 and 2000, and then the difference in AF between the two years.

For the mean number of children, the 7% risk reduction was converted into a risk increase. For breast cancer, AFs for each year were calculated using the difference in mean number of children in parous women. For ovarian cancer, we used the difference in mean number of children in all women.

Changes in breast and ovarian cancer incidence and mortality associated with changes in reproductive factors over time are displayed in Tables B9.2 and B9.3. Overall, changes in reproductive factors over 20 years were involved in 6.7% of breast cancers and in 0.38% of ovarian cancers.

5. Discussion

The 6.7% increase in breast cancers associated with reproductive factors between 1980 and 2000 is essentially due to higher age at first birth; the slight decrease in the proportion of nulliparous women and the modest revival of breastfeeding had opposite effects on breast cancer risk, but the effect is too small to counterbalance the rise in risk associated with age at first birth.

In view of the uninterrupted increase in breast cancer incidence that has taken place in many countries since the 1950s, the associations found in this report between changes in reproductive factors and breast cancer incidence may appear modest. The apparently limited contribution of reproductive factors is probably due to not having a long enough time interval for the comparisons. For instance, early menarche is associated with increased breast cancer risk. In France, as in most industrialized countries, age at menarche has substantially decreased over time, from a mean age of 16 years in the second part of the 18th century to 12.6 in 1994 (de la Rochebrochard, 1999, 2000). According to a model developed by Ducros and Pasquet (1978) for France, over twenty years, mean age at menarche changed by about 0.35 years. This small difference over 20 years does not fully reflect the major changes in this reproductive factor that took place over generations, and the same would probably apply for the other reproductive factors. Furthermore, it is worth noting that the current epidemic of obesity in girls less than 10 years old will contribute to a further decrease in age at menarche, which may in turn further increase lifetime risk of breast cancer.

Our results indicate that changes in reproductive factors cannot explain all the increase in breast cancer incidence observed during recent decades. Increased disease awareness, mammographic screening and use of hormone replacement therapy have probably played more important roles.

Different rates of breast cancer incidence between countries may be explained by variations in reproductive factors such as the number of children per woman, age at first birth and duration of breastfeeding, which can vary greatly between populations.

At the individual level, differences in reproductive factors between women may account for meaningful differences in individual risk of breast cancer (Pathak et al., 2000): a woman who has a single child after 35 years of age and does not breastfeed has about a two-fold increase in lifetime risk of breast cancer compared with a woman who has more than three children, the first one born before she is 20 and who breastfeeds each baby for at least six months. Within a country, however, reproductive behaviours tend to homogenize and most women have similar levels of reproductive risk factors. An example is the persistent time-trend towards two children per woman in France (Toulemon and Mazuy, 2001). As a result, differences in breast cancer risk associated with reproductive factors at the individual level do not have much impact on short-term variations in breast cancer incidence in a country. Data by birth cohort on reproductive factors and on breast cancer mortality going back to the mid-19th century would allow us to estimate the impact of changes in reproductive factors in the longer term,

say between the years 1950 and 2000, but such data probably do not exist.

References

Bac C, Legendre F, Mahieu R, Thibault F. Fécondité et âge de fin d'études en France depuis 1975. L'évolution au fil des générations des facteurs traditionnels de la fécondité. Recherche et Prévisions, 79 (mars 2005):21–35.

Blondel B, Bréart G, du Mazaubrun C, et al. La situation périnatale en France: évolution entre 1981 et 1995. J Gynecol Obstet Biol Reprod 1997;26:770–780.

Blondel B, Norton J, du Mazaubrun C, et al. Évolution des principaux indicateurs de santé périnatale en France métropolitaine entre 1995 et 1998: résultats des enquêtes nationales périnatales. J Gynecol Obstet Biol Reprod 2001;30:552–564.

CGHFBC. Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and breastfeeding: collaborative reanalysis of individual data from 47 epidemiological studies in 30 countries, including 50302 women with breast cancer and 96973 women without the disease. Lancet 2002;360:187–195.

de la Rochebrochard E. Les âges à la puberté des filles et des garçons en France. Mesure à partir d'une enquête sur la sexualité des adolescents. Populations 1999;6:933-972.

de la Rochebrochard E. Age at puberty of girls and boys in France. Measurement from a survey on adolescent sexuality. Populations 2000;12:51-80.

Ducros A, Pasquet P. Évolution de l'âge d'apparition des premières règles (ménarche) en

France. Biométrie Humaine 1978;13 (1-2):35-43

Harvard Report on Cancer Prevention. Volume 1: Causes of human cancer. Cancer Causes Control. 1996; Suppl 1:S3–59

Layde PM, Webster LA, Baughman AL, et al. The independent association of parity, age at first full term pregnancy, and duration of breastfeeding with the risk of breast cancer. J Clin Epidemiol 1989;42:963–973.

Lesné E, Bravelle, Weill-Spire M. A propos de l'allaitement maternel dans les départements de la Seine et de la Seine-et-Oise pour les années 1949, 1951, 1952. Sem Médicale 1953;27:401–404.

Madigan MP, Ziegler RG, Benichou J, et al. Proportions of breast cancer cases in the United States explained by well-established risk factors. J Natl Cancer Inst 1995;87:1681–1685.

Pathak D, Osuch JR, He J. Breast carcinoma etiology: current knowledge and new insights into the effects of reproductive and hormonal risk factors in black and white populations. Cancer 2000;88:1230–1238.

Pike MC, Krailo MD, Henderson BE, et al. "Hormonal" risk factors, "breast tissue age" and the age-incidence of breast cancer. Nature 1983;303:767–770.

Pike MC, Spicer DV, Dahmoush L, Press MF. Estrogens, progestogens, normal breast cell proliferation, and breast cancer risk. Epidemiol Rev 1993;15:17–35.

Rollet C. Histoire de l'allaitement en France : pratiques et représentations. Institut des Formations Co-Naître, Novembre 2005.

Toulemon L. Combien d'enfants, combien de frères et sœurs depuis cent ans? Population et Sociétés 2001:374.

Toulemon L. La fécondité en France depuis 25 ans. Paris, Haut Conseil de la population et de la famille (HCPF). Janvier 2003. http://www.ladocumentationfrancaise.fr/rapports-publics/034000116/index.shtml

Toulemon L, Mazuy M. Les naissances sont retardées mais la fécondité est stable. Population 2001;56:611–644.

Ursin G, Bernstein L, Pike MC. Breast cancer. Cancer Surveys, 1994;19/20:241–264.

Table B9.1 - Change in reproductive factors between 1980 and 2000 in France, and corresponding changes in AF*

Reproductive factor	Exposure in 1980	Exposure in 2000	RR		AF 1980	AF 2000	Difference in AF
% Nulliparous	16.2%	11.9%	1.36		5.5%	4.1%	–1.40%
Mean number of children per parous woman (for breast cancer)	2.61	2.47	0.930	Risk reduction per child	–20.9%	–19.6%	1.22%
Mean number of children per woman (for ovarian cancer)	2.19	2.17	0.870	Risk reduction per child	–35.7%	–35.3%	0.38%
% with age at first birth > 29 years	25%	41.0%	1.67		14.3%	21.6%	7.20%
Number of months breastfeeding (cumulative for all children)	3.4	4.2	0.957	Risk reduction per 12 months of breastfeeding	–1.3%	–1.6%	–0.30%
Total change in AF for breast cancer							6.7%

*AF calculated with ordered RRs for nulliparity and age at first birth >29 years old. AF calculated with continuous RR (after napierian logarithmic transformation) for numbers of children and months of breastfeeding (see Methods Section A1 for details)

Table B9.2 – Estimation of the number of breast and ovarian cancers cases and deaths in France in 2000 attributable to changes in reproductive risk factors between 1980 and 2000

INCIDENCE				
		Females		
Cancer		**N**	**AF**	**No. attributable**
Ovary – Number of children	Ovary	4488	0.38%	17
Breast – Nulliparity	Breast ≥ 35 years	41057	–1.40%	–576
Breast – Number of children	Breast among parous women	34685	1.22%	424
Breast – Breastfeeding	Breast among parous women	34685	–0.30%	–103
Breast – Age at first birth	Breast among parous women	34685	7.20%	2498
Breast cancer cases attributable to change in reproductive factors				2243
		Breast cancer	%	5.4%
		All cancers	Total	2260
			%	1.93%
MORTALITY				
		Females		
Cancer		**N**	**AF**	**No. attributable**
Ovary – Number of children	Ovary	3210	0.38%	12
Breast – Nulliparity	Breast ≥ 35 years	10868	–1.40%	–152
Breast – Number of children	Breast among parous women	9181	1.22%	112
Breast – Breastfeeding	Breast among parous women	9181	–0.30%	–27
Breast – Age at first birth	Breast among parous women	9181	7.20%	661
Breast cancer cases attributable to change in reproductive factors				594
		Breast cancer	%	5.4%
		All cancers	Total	606
			%	1.06%

Figure B9.1 – Distribution of women according to the final number of children they had, by age in the year 2000
(data from INED)

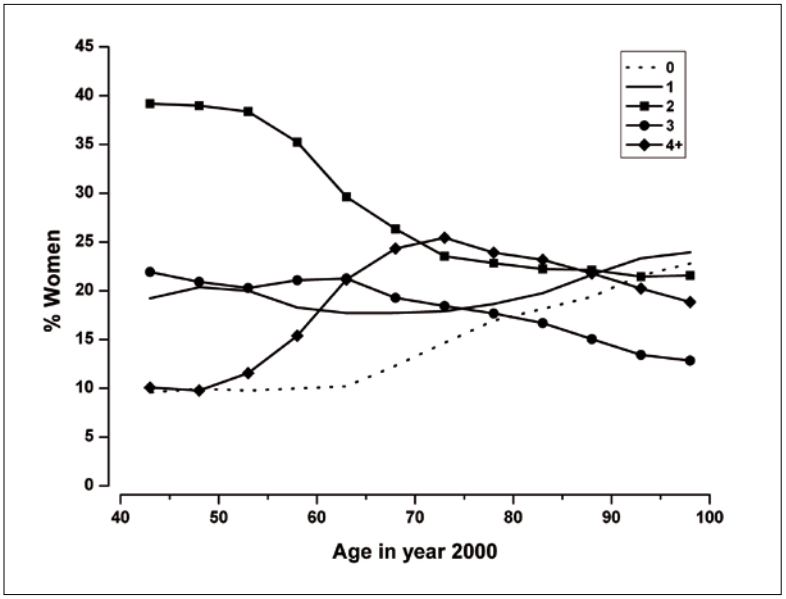


Figure B9.2 – Mean number of children per French woman 38 years old and more according to birth cohort
(estimated using data from INED)

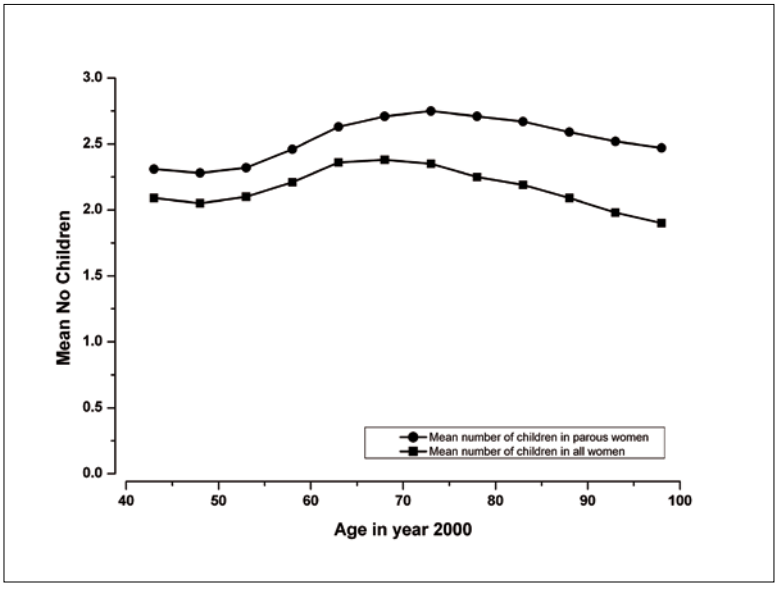


Figure B9.3 – Proportion of French parous women who had their first child at 30 years old more (data from INED)

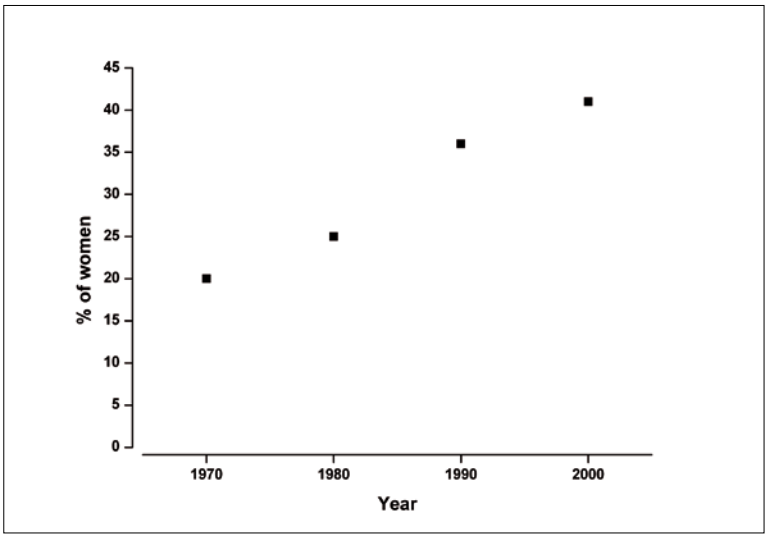
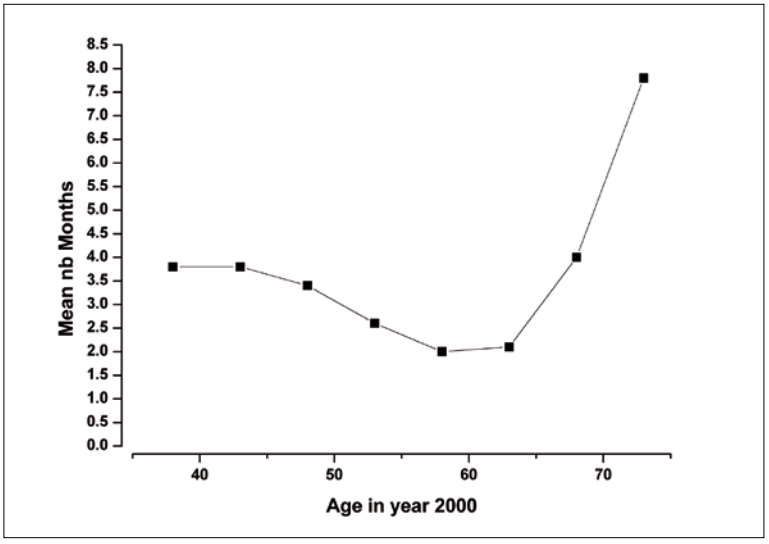


Figure B9.4 – Estimated mean number of months of breast feeding of parous women in France according to age in year 2000 (see text for data sources)**. Means are calculated considering all children women had.**



Section B10: Water, air, soil and food pollutants

I. Introduction

In the present study, we considered pollutants for which a causal association with human cancer has been established. We calculated an AF for second-hand smoke and indoor exposure to radon (Boffetta and Nyberg, 2003). Cancer risk from residential exposure to asbestos is discussed but no AF is provided. Residential exposure to radon is discussed in Section D1, but estimates of the number of lung cancers due to residential radon are not provided because of uncertainties in the cancer risk associated with low doses of ionizing radiation (see Section D1). For a number of other pollutants, the evidence of a role in human cancer is only suggestive; these are reviewed in Section D3 and no estimate of AF was made.

II. Second-hand smoke

1. Definition of exposure

Second-hand smoke, i.e., sidestream smoke and exhaled mainstream smoke inhaled by non-smokers, is an established human lung carcinogen (Hackshaw et al., 1997; IARC, 2004). Evidence for a carcinogenic risk from exposure during childhood is not conclusive. Adult exposure occurs mainly at home - primarily from the spouse - and in the workplace. Minor sources of exposure include public settings such as bars and restaurants. In this estimate, we included only adult exposure to second-hand smoke at home and in the workplace. The alternative exposure scenario is that of no exposure.

2. Data used for RR estimates

We used an RR of lung cancer in never-smokers associated with second-hand smoking from the spouse or at the workplace from a meta-analysis reported in IARC Monograph Vol. 83 (IARC, 2004). In this meta-analysis, risks of 1.37 and 1.24 were found for exposure to second-hand smoke from the spouse for men and women, respectively. For exposure at the workplace, the relative risk was 1.19 for women and 1.12 for men. We considered spousal and workplace exposures to second-hand smoke as independent risk factors for estimation of the attributable fraction.

3. Data used for exposure prevalence

Based on the data of the European multicentric study on risk of lung cancer and involuntary smoking (Boffetta et al., 1998), the proportion of never-smokers ever exposed to smoke from the spouse was 12.8% in men and 62.7% in women; corresponding proportions for workplace exposure were 56.7% in men and 52.8% in women. These exposures were considered as independent in the estimation of the attributable fraction.

4. Calculation of AFs

Because relative risks and prevalence are relevant only to never-smokers, we applied AFs to the number of lung cancer cases that occurred among men and women who had never smoked.

Table B10.1 displays details of the calculations

to estimate the lung cancers due to secondhand smoking among never-smokers in France in 2000.

(i) Using the prevalence data from Section B1 on tobacco smoking, we first calculated the proportions of never-smokers.

(ii) We then computed AFs for lung cancer among non-smokers, using the aforementioned RR and exposure data from Boffetta et al. (1998), which yielded an AF for second-hand smoking from the spouse among never-smokers of 4.5% in men and 13.1% among women; the AF for second-hand smoking in the workplace among never-smokers was 9.1% among women.

(iii) We then derived the number of lung cancers in never-smokers, assuming a proportional distribution of non-smoking-related lung cancers among ever- and never-smokers.

(iv) Finally, we calculated the numbers of lung cancers among never-smokers attributable to second-hand smoking, i.e., 43 in men and 174 in women. We performed similar computations for deaths from lung cancer that yielded 38 deaths in males and 161 deaths in females.

III. Residential exposure to asbestos

Asbestos is an established occupational carcinogen (see Section B4). Residential exposure occurs following release of fibres from mines, manufacturing plants and degradation of asbestos-containing materials. A meta-analysis that included studies of populations experiencing heavy residential asbestos exposure estimated an RR for pleural mesothelioma of 3.5 (95% CI 1.8–7.0) (Bourdes et al., 2000; Boffetta and Nyberg, 2003). The corresponding RR for lung cancer was 1.1 (95% CI 0.9–1.5).

According to a model developed by WHO in 1987, 5% of the European population experienced residential exposure to asbestos. However, this model included mainly circumstances of very low exposure and was thus likely to overestimate the proportions of populations experiencing exposure circumstances comparable to those prevailing in studies that were included in the meta-analysis of Bourdes et al. (2000). In order to assess the order of magnitude of the problem, we combined the RR mentioned for pleural mesothelioma above with a proportion of exposure of 1%, which probably represents an overestimate. In this case, a total of 2.4% of pleural mesothelioma would be attributable to residential exposure to asbestos. In 2000, this corresponded to 16 cases among men and 5 cases among women. Corresponding figures for mortality were 15 and 4, respectively. We made no estimate for lung cancer as no causal association has been demonstrated between residential asbestos and this cancer.

IV. Overall estimate

Table B10.1 summarizes the estimates of the numbers of lung cancer deaths due to second-hand smoking in France in the year 2000. The same type of calculation performed with lung cancer incidence data reveals 103 cases in men and 174 cases in women attributable to this pollutant. For residential asbestos, in year 2000, there were 16 and 5 cases of pleural cancer in men and women respectively, and 15 and 4 deaths, respectively. Overall, 0.07% of all cancers in men and 0.15% in women would be attributable to exposure to pollutants recognized as being human carcinogens. Corresponding estimates for cancer mortality were 0.12% of cancer deaths in men and 0.29% in women.

V. Discussion

1. Methodological considerations

Epidemiology has low sensitivity for identifying cancer risks from pollutants; misclassification of exposure and limited statistical power to detect small risks are the main reasons for false negative results. In a few cases, attempts have been made to correct for these sources of bias (e.g., effect of regression dilution in the estimate of RR from indoor radon exposure (Darby et al., 2005)). These problems are common to other areas of epidemiology (e.g., studies on diet and cancer).

On the other hand, false positive results are also possible, because of uncontrolled confounding and reporting bias. The role of the latter source of bias is often underestimated; in fact, many associations that have been reported between a pollutant and human cancer have never been replicated in further studies

with large samples, better study designs and more adequate control of confounding factors. To illustrate this problem, Figure B10.1 reports the cumulative evidence of an association between serum level of DDE (dichlorodiphenyldichloroethylene), the main metabolite of DDT (dichlorodiphenyltrichloroethane), and breast cancer risk. In 1993, a cohort study reported a strong relative risk among women with elevated levels of DDE (Wolff et al., 1993). However, these early results were not confirmed by subsequent larger studies (Krieger et al., 1994; Hoyer et al.,1998; Dorgan et al., 1999; Helzlsouer et al., 1999; Ward et al., 2000; Wolff et al., 2000; Laden et al., 2001), and it is impossible to draw any conclusion from the overall evidence as to a possible association between exposure to DDE and breast cancer.

Because of these limitations, caution is needed in interpreting associations between pollutants and cancer risk; this is reflected in the conservative approach we have followed in considering only pollutants for which a causal association with cancer is firmly established.

2. Second-hand smoking

Exposure to second-hand smoke from the spouse is not independent of that in the workplace, and some of the attributable cases may overlap. Exclusion of other sources of second-hand smoke may have resulted in a small underestimation of the AF. Similarly, it is plausible that a small number of lung cancers occur as a consequence of second-hand smoke exposure among smokers. However, relative risks of lung cancer in current or past smokers are so high compared to relative risks associated with second-hand smoking that the real impact of second-hand smoking on the lung cancer risk among smokers is negligible. The evidence linking second-hand smoke to other cancers is inconclusive (IARC, 2004).

3. Pollutants and tobacco smoking

The fact that most pollution-related cancers – at least in France – originate in the lung gives a special perspective to the problem, as most of these cancers occur in smokers, and therefore, many (or even most) of them could be prevented by smoking cessation. This consideration is not intended to diminish the importance of the problem from a public health perspective or the need to reduce harmful and involuntary exposures, but further emphasizes the role of tobacco as a human carcinogen and its importance as a main target of cancer prevention.

References

Boffetta P, Nyberg F. Contribution of environmental factors to cancer risk. Br Med Bull 2003;68:71–94.

Boffetta P, Agudo A, Ahrens W, et al. Multicenter case-control study of exposure to environmental tobacco smoke and lung cancer in Europe. J Natl Cancer Inst 1998;90:1440–1450.

Bourdes V, Boffetta P, Pisani P. Environmental exposure to asbestos and risk of pleural mesothelioma: review and meta-analysis. Eur J Epidemiol 2000;16:411–417.

Darby S, Hill D, Auvinen A, et al. Radon in homes and risk of lung cancer: collaborative analysis of individual data from 13 European case-control studies. BMJ 2005;330:223

Dorgan JF, Brock JW, Rothman N, et al. Serum organochlorine pesticides and PCBs and breast cancer risk: results from a prospective analysis (USA). Cancer Causes Control 1999;10:1–11.

Hackshaw AK, Law MR, Wald NJ. The accumulated evidence on lung cancer and environmental tobacco smoke. BMJ 1997;315:980–988.

Helzlsouer KJ, Alberg AJ, Huang HY, et al. Serum concentrations of organochlorine compounds and the subsequent development of breast cancer. Cancer Epidemiol Biomarkers Prev 1999;8:525–532.

Hoyer AP, Grandjean P, Jorgensen T, et al. Organochlorine exposure and risk of breast cancer. Lancet 1998;352:1816–1820.

International Agency for Research on Cancer. Involuntary tobacco smoke. IARC Monographs on the Evaluation of the Carcinogenic Risks to Humans, Vol. 83. Tobacco Smoking and Involuntary Tobacco Smoke. .Lyon, IARC, 2004, pp 1191–413.

Krieger N, Wolff MS, Hiatt RA, et al. Breast cancer and serum organochlorines: a prospective study among white, black, and Asian women. J Natl Cancer Inst 1994;86:589–99.

Laden F, Hankinson SE, Wolff MS, et al. Plasma organochlorine levels and the risk of breast cancer: an extended follow-up in the Nurses' Health Study. Int J Cancer 2001;91:568–574.

Valleron AJ, Bignon J, Hughes JM, et al. Low dose exposure to natural and man made fibres and the risk of cancer: towards a collaborative European epidemiology.

Report of a workshop held in Paris , 10–12 June, 1991. Br J Ind Med 1992;49:606–614.

Ward EM, Schulte P, Grajewski B, et al. Serum organochlorine levels and breast cancer: a nested case-control study of Norwegian women. Cancer Epidemiol Biomarkers Prev 2000;9:1357–1367.

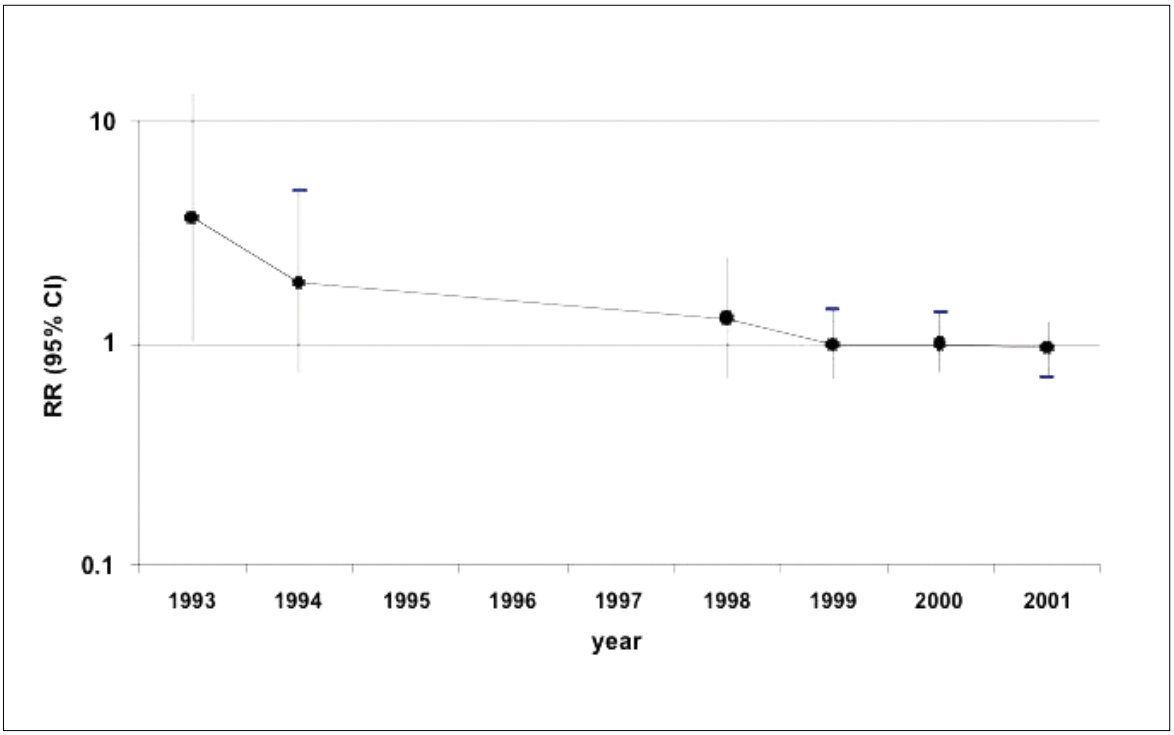
Wolff MS, Toniolo PG, Lee EW, et al. Blood levels of organochlorine residues and risk of breast cancer. J Natl Cancer Inst 1993;85:648–652.

Wolff MS, Berkowitz GS, Brower S, et al. Organochlorine exposures and breast cancer risk in New York City women. Environ Res 2000;84:151–161.

Table B10.1 – Estimation of the number of lung cancer deaths among never-smokers in France in 2000 attributable to second-hand smoking

		Males	Females
Prevalence of tobacco smoking (from Section B1)			
	% Current smokers (a)	48.2%	30.4%
	% Former smokers (b)	27.7%	14.0%
	% Ever-smokers (c) = (a) + (b)	75.9%	44.4%
	% Never-smokers (d) = 100 – (c)	24.1%	55.6%
AF estimate for second- hand smoking among never-smokers			
	Exposure to smoking spouse		
	% Never-smokers exposed to smoking spouse (see text)	12.8%	62.7%
	RR for lung cancer (see text)	1.37	1.24
	AF (e)	4.5%	13.1%
	Exposure to smoking at workplace		
	% Never-smokers exposed to smoking at workplace (see text)	56.7%	52.8%
	RR for lung cancer (see text)	1.12	1.19
	AF (f)	6.4%	9.1%
Number of deaths attributed to second-hand smoking			
	Total number of lung cancer deaths in 2000 (g)	20585	4246
	Lung cancer deaths in ever-smokers attributable to smoking (h)	17085	2939
	Lung cancer deaths non-attributable to smoking (i) = (g) – (h)	3500	1307
	Lung cancer deaths among never-smokers (j) = (i)*(d)	843	727
	Lung cancer deaths attributable to second-hand smoking from spouse among never-smokers (j)*(e)	38	95
	Lung cancer deaths attributable to second-hand smoking at workplace among never-smokers (j)*(f)	54	66
	Total number of lung cancer deaths attributed to second-hand smoking	92	161

Figure B10.1 – Cumulative meta-analysis of risk of breast cancer and exposure to DDE.
Meta-relative risks (with 95 % CI), by year of publication of initial (Wolff et al., 1993) and five subsequent reports



Synthesis of results

Section C1: Attributable fractions : summary and sources of uncertainty

1. Summary of attributable fractions

Tables C1.1 and C1.2 display the overall numbers of incident cancer cases and deaths attributable to risk factors evaluated in this report. It is tempting to sum the figures in these tables to obtain the total proportions of cancer cases and deaths that could be attributed to established risk factors. The percentages presented in Tables C1.1 and C1.2 reflect the effect of removing one cause of cancer independently of other causes. But because cancers have multiple causes, the same cancers can be attributed to more than one cause, so summing the figures in these tables would overestimate the global burden of cancer attributable to the established risk factors. Section C2 on interactions between risk factors provides a more adequate interpretation of the proportions of cancer attributable to each risk factor taking into account the joint effect of two or more of them.

Tobacco smoking and alcohol drinking are by far the main risk factors for cancer in France. The role of infectious agents as causal agents for cancer may be greater than suggested by our estimates because it is likely that many infectious agents involved in cancer remain unknown and the available data on exposure to infectious agents known to be associated with cancer remain imprecise (see Sections B3, E1 and E2). Current scientific knowledge suggests that all other factors would account for a relatively small proportion of all cancers cases and death, but it needs to be stressed that some factors like diet and air pollution deserve further studies for establishing their exact role in cancer occurrence (see Section D3 for detailed discussion of these aspects).

Because of the importance of tobacco smoking, we estimated the specific attributable fraction, separating ever-smokers (current smokers and former smokers) from never-smokers (Table C1.3). The method used was the following:

(i) We first distributed the observed number of cancers in 2000 by cancer site using the attributable fractions calculated in Section B1. For example, among the 3250 deaths in men from bladder cancer, we attributed 1715 to tobacco. We therefore considered these cases as coming from the population of ever-smokers.

(ii) The remaining deaths were distributed according to the prevalence of tobacco smoking, for example, 76% of the remaining 1535 bladder cancers were allocated to the ever-smokers (1165 deaths) and 24% were allocated to the never-smokers (370 deaths).

(iii) The attributable fractions associated with other causes of cancers (calculated in Sections B2 to B10) were applied to these denominators sorted by smoking status to estimate the number of cases attributable to each cause. Then the numbers of deaths according to smoking status were summed across cancer sites.

Applying the method further developed in Section C2 on interactions, we estimated that 50.6% of cancers in ever-smoker men were attributable to a

known cause. In male never-smokers, only 14.0% of cancers could be attributed to a known cause. For female ever-smokers, 31.8% of cancers were associated with a known cause, compared with 15.6% among female never-smokers. Among ever-smokers, cancers associated with tobacco smoking in men represent 67.3% of cancers for which a cause of cancer was attributed and in women 53.8%.

In this analysis, we grouped together current and former smokers. However, because of the lower attributable fraction associated with tobacco in former smokers, the attributable fractions for current smokers should be higher than shown in Table C1.3.

Moreover, no attempt was made to take into account potential interactions with other factors. As mentioned in the next section on interactions (Section C2), causes such as alcohol and occupation have interactions with tobacco smoking, and hence, for full appreciation of the burden of tobacco smoking, a factor of interaction should be included to increase the percentage of cancer associated with tobacco.

It is also worth noting that breast cancer and prostate cancer are included in the denominators, although tobacco smoking is not associated with their occurrence. If these cancers were not included in the denominators, the result would be that more than 60% of cancer in ever-smokers would be attributable to an established risk factor.

2. Sources of uncertainty

We have provided our best estimates of the proportions of specific cancers attributable to specific causes in French men and women in 2000. The uncertainty surrounding these estimates is substantial, and arises from several sources (Table C1.4). In some cases, it would be possible to quantify the uncertainty (e.g., confidence intervals of relative risks and exposure frequencies; alternative scenarios of exposures), while in other cases quantification would be either very difficult (e.g., modelling lag time to provide a biologically-driven estimate of cumulative exposure) or practically impossible (e.g., RR and exposure frequency data from non-comparable populations).

Some authors of systematic reviews of the contributions of different causes to human cancer have provided 'acceptable ranges' around their point estimates. In particular, this was done by Doll and Peto in their 1981 and 2005 publications (Doll and Peto, 1981, 2005). The authors, however, did not provided a rationale for deriving such ranges or intervals, although one appreciates that they intended to reflect the global degree of uncertainty for a particular cancer or risk factor (Table C1.5). For example, Doll and Peto (2005) provided range widths of ± 10% in the case of tobacco and ± 40% in the case of diet: this clearly reflects the stronger evidence available for the former as compared to the latter risk factor, which we have also discussed elsewhere in this report.

To be consistent with our strictly quantitative approach, however, we decided not to provide such ranges, which would necessarily be subjective. We outline below the difficulties in quantifying uncertainty levels of AFs.

First, uncertainty can proceed from known statistical considerations. Most prevalence data and relative risks used in this report were presented with their respective confidence interval or an indication of variability such as population size in surveys. We used a Delta method (Klein, 1953) to estimate uncertainty intervals for the AF estimates in Tables C1.1 and C1.2. Based on Levin's formula, the estimated variance of the AF is of the form:

$$V(AF) = \frac{(e^{\beta} - 1)^2 V(P) + (Pe^{\beta})^2 V(\beta)}{\left[P(e^{\beta} - 1) + 1\right]}$$

where *P* is the prevalence of exposure and ß defined as ln(RR).

When prevalence data were available for the whole population (such as for alcohol consumption or average indoor radon exposure), we considered that the variance of the prevalence data was null.

For EBV infection, HPV infection (for cervix uteri cancer) and asbestos exposure, we directly used an estimate of AF from the literature. No uncertainty interval was available for these causes. Estimation of uncertainty intervals for summary numbers of cases and deaths attributable to infection and to occupational exposure was performed under the hypothesis of no variability for the AF for EBV infection, HPV infection (for cervix uteri cancer) and asbestos exposure.

Table C1.6 presents the number of deaths attributed to each cause with the corresponding uncertainty interval calculated by the Delta method.

Second, various sources of errors in relative risks could have influenced our estimates. Even if a

cause of cancer is clearly established by the IARC, the relative risks available in the literature could be biased towards greater or lower values due to misclassification or selection biases. The use of relative risk estimates from meta-analyses dilutes the effects of biases from a single study. Prevalence data are also highly susceptible to biases, since it is well established that any population-based survey tries to infer values for the whole population, although some populations can hardly be included in survey campaigns. These populations are also known to be more highly exposed to various risk factors such as tobacco or alcohol than the groups included in the surveys. Selection biases (in epidemiological studies or in surveys) cannot be adjusted for by statistical methods. Combining biases in relative risk with biases in exposure prevalence would contribute to increasing the bias in the estimate of AF.

For these reasons, as far as the available data allowed, we used RRs from the most appropriate meta-analyses or epidemiological studies and exposure prevalence data from studies specifically designed to assess exposures. Hence, because we used the "best" estimate of relative risk and prevalence measured with the most suitable methodology, our estimates of AFs were the best that could currently be calculated.

Third, the exposure prevalence data and relative risks were extracted independently. The estimation of AFs requires the use of similar definitions and units of exposure. A small shift in the measurement between the two independent sources could produce a bias in the estimation of AFs. This is especially true if there is misclassification of subjects who should have been classified as unexposed (Wacholder et al., 1994). This could have affected the estimate of the AF for infection, because detection tests for infection may be less sensitive when used on wide populations than tests used in studies designed for accrual of a maximum of infected persons (such as case–control studies). Underestimation of AFs for physical inactivity could also result if the prevalence of inactivity is underestimated; studies on physical activity detail the various types of physical activity and are therefore less susceptible to underreporting, while in surveys it is highly probable that individuals will tend to give a "politically correct" answer. For similar reasons, our occupational prevalence estimates might be higher than the true levels because we used prevalence data from identifiable populations rather than from less exposed populations (e.g., the difference between populations surveyed by the different SUMER surveys in France; see Section B4).

Fourth, our estimates are based on an *a priori* lag time of 15 years, which allows only a crude estimate of AFs. Cancer occurring in 2000 could be caused by exposure that occurred over any period from 1900 to 2000. For example, lung cancer occurring in older age-groups can be attributed to exposure to tobacco starting before 1950, when the prevalence was totally different from what it is now. This arbitrary lag-time is currently the most conservative and plausible value and it produces an average estimate of AFs based on the assumption of no major change in prevalence before or after this time. For most causes such as tobacco, alcohol and infection, of which prevalence in the population tends to change only slowly, the effect of choice of lag time on the AF estimate is expected to be low.

3. Conclusion

In summary, about 35% of all cancer deaths are potentially avoidable because they are due to tobacco, excess in alcohol intake, infectious agents, obesity, lack of physical activity, taking of hormones and excessive sun exposure. Better implementation of preventive regulations at the workplace could also further decrease cancer deaths due to occupational factors. The contribution of the fight against pollutants in cancer control may much smaller, but there is a need for further research on this topic.

References

Doll R, Peto R. The causes of cancer: quantitative estimates of avoidable risks of cancer in the United States today. J Natl Cancer Inst 1981;66:1191–308.

Doll R, Peto R. Epidemiology of cancer. In: Oxford Textbook of Medicine, 4th edition, Oxford, Oxford University Press, 2005.

Klein LR. A Textbook of Econometrics. New York, Row, Peterson and Company, 1953.

Wacholder S, Benichou J, Heineman EF, et al. Attributable risk: advantages of a broad definition of exposure. Am J Epidemiol 1994;140:303-309

Table C1.1 – Numbers of cancer cases and proportions attributed to various factors in France in the year 2000

	Males		Females		Both sexes	
Risk factors*	**Number**	**% of all cancers**	**Number**	**% of all cancers**	**Number**	**% of all cancers**
Tobacco	43 466	27.0	7095	6.1	50 561	18.2
Alcohol	17 398	10.8	5272	4.5	22 670	8.1
Infectious agents	4206	2.6	4871	4.2	9077	3.3
Physical inactivity	780	0.5	5541	4.7	6321	2.3
Obesity and overweight	2249	1.4	3899	3.3	6148	2.2
Ultraviolet light	2380	1.5	3234	2.8	5614	2.0
HRT-OC	–	–	5828	5.0	5828	2.1
Occupation	4013	2.5	314	0.3	4327	1.6
Reproductive factors †	–	–	2260	1.9	2260	0.8
Pollutants ‡	119	0.07	179	0.15	298	0.1

HRT-OC: Hormone replacement therapy and oral contraceptive use

* Ranked according to number of cancer cases in both sexes

† Change in reproductive factors between 1980 and 2000

‡ Several factors such as air particulate matter were not taken into account (see Section D3). If 50% of French population was exposed to air particulate matter concentrations associated with an increase in lung cancer risk of 7%, then in this table, 0.83% of all cancers in men and 0.4% of all cancers in women would be attributable to pollutants

Table C1.2–Numbers of cancer deaths and proportions attributed to various factors in France in the year 2000

	Males		Females		Both sexes	
Risk factors*	**Number**	**% of all cancers**	**Number**	**% of all cancers**	**Number**	**% of all cancers**
Tobacco	28 934	33.4	5449	9.6	34 383	23.9
Alcohol	8188	9.4	1692	3.0	9880	6.9
Infectious agents	2867	3.3	2511	4.4	5378	3.7
Occupation	3183	3.7	256	0.5	3439	2.4
Obesity and overweight	995	1.1	1321	2.3	2316	1.6
Physical inactivity	427	0.5	1812	3.2	2239	1.6
HRT-OC	–	–	1239	2.2	1239	0.9
Ultraviolet light	548	0.6	499	0.9	1047	0.7
Reproductive factors †	–	–	606	1.1	606	0.4
Pollutants ‡	107	0.12	165	0.3	272	0.2

HRT-OC: Hormone replacement therapy and oral contraceptive use

* Ranked according to number of cancer deaths in both sexes

† Change in reproductive factors between 1980 and 2000

‡ Several factors such as air particulate matter were not taken into account (see Section D3). If 50% of French population was exposed to air particulate matter concentrations associated with an increase in lung cancer risk of 7%, then in this table, 0.83% of all cancer deaths in men and 0.4% of all cancer deaths in women would be attributable to pollutants

Table C1.3–Proportions of cancer deaths attributed to various factors according to smoking status in the absence of interaction between tobacco and other factors

	Males		Females	
	Ever-smokers*	Never-smokers	Ever-smokers*	Never-smokers
Risk factors	**AF (%)**	**AF (%)**	**AF (%)**	**AF (%)**
Tobacco	39.7	–	19.3	–
Alcohol	10.0	6.7	2.9	3.0
Infection	3.1	3.0	4.8	3.9
Obesity and overweight	1.1	1.4	2.1	2.5
Inactivity	0.4	0.7	2.8	3.5
Ultraviolet light	0.5	0.9	0.7	0.9
HRT-OC	–	–	1.9	2.4
Occupation	4.0	1.9	0.7	0.3
Pollutants	0.1	0.05	0.5	0.1
Total §	**50.6**	**14.0**	**31.8**	**15.6**

HRT-OC: Hormone replacement therapy and oral contraceptive use
* Current or former smokers
§ The overall AF was estimated considering multiplicative interaction as described in Section C2

Table C1.4 - Sources of uncertainty in the estimation of attributable cancers

Component of AF	Source of uncertainty	Explanation, examples	Quantitative aspects
Relative risk	Random error	Relative risks (both in individual studies and in meta-analyses) are subject to random variability that depends mainly on the size of the study populations	Quantifiable (confidence interval)
	Bias	Relative risks may be biased because of residual confounding and lack of proper control of bias in the original studies	Qualitative assessment possible; quantification difficult
Exposure frequency	Random error	Exposure frequency data are subject to random variability, that depends on the size of the study populations	Quantifiable (confidence interval)
	Bias	Surveys and other studies on exposure frequency may be subject to selection and information bias	Qualitative assessment possible; quantification difficult
Correspondence of relative risk and exposure data	Geographic correspondence	Relative risks and/or exposure frequency data derived from different populations and/or from populations other than that under study	Quantification difficult
	Temporal correspondence	Relative risks and/or exposure frequency data refer to different time periods and/or populations other than that under study; exposure data refer to a time period irrelevant for the carcinogenic effect of the risk factor	Modelling and alternative exposure scenarios feasible
	Substantive correspondence	Relative risks and exposure frequency data refer to different entities (even partially so)	Quantification difficult

Table C1.5. - Factors applied by Doll and Peto (2005) to calculate 'acceptable ranges' of estimates of attributable factors in United Kingdom

Risk factor	Uncertainty factor
Tobacco	1.1
Alcohol	1.33
Ionizing radiation	1.2
Ultraviolet light	1
Infection	3
Medical drugs	NA*
Occupation	2.5
Pollution	2.5
Diet	1.4
Reproduction	1.33
Physical inactivity	NA*

NA: Not available

* In the case of medical drugs and physical inactivity, the best estimate is < 1% and the acceptable range 0–1%

Table C1.6 – Uncertainty intervals (UI) of number and proportion of deaths associated with various factors based on a 95% CI of RRs and exposure frequency estimates

	Males					Females			
Cause	**No.**	**95% UI**	**%**	**95% UI**		**No.**	**95% UI**	**%**	**95% UI**
Tobacco	28 934	[27 219–30 649]	33.4	[31.4–35.3]		5449	[4930–5968]	9.6	[8.7–10.5]
Alcohol	8188	[7578–8797]	9.4	[8.7–10.1]		1692	[1469–1914]	3.0	[2.6–3.4]
Infection	2867	[2252–3482]	3.3	[2.6–4]		2511	[2310–2712]	4.4	[4.1–4.8]
Occupation	3183	[2753–3612]	3.7	[3.2–4.2]		258	[224–291]	0.5	[0.4–0.5]
Obesity and overweight	995	[801–1189]	1.1	[0.9–1.4]		1321	[1212–1429]	2.3	[2.1–2.5]
Physical inactivity	427	[152–702]	0.5	[0.2–0.8]		1812	[808–2816]	3.2	[1.4–4.9]
HRT-OC	–	–	–	–		1239	[1089–1390]	2.2	[1.9–2.4]
Ultraviolet light	548	[469–627]	0.6	[0.5–0.7]		499	[427–571]	0.9	[0.8–1]
Pollutants	107	[0–269]	0.12	[0–0.3]		165	[117–214]	0.3	[0.2–0.4]

HRT-OC: Hormone replacement therapy and oral contraceptive use

Section C2: Interactions between cancer risk factors

Cancer arises through inherited or acquired genetic alterations in multiple pathways involved in cell replication, proliferation and growth (Hanahan and Weinberg, 2000). As a first approximation, each such alteration can be caused by inherited conditions, endogenous factors or exogenous carcinogens, including the risk factors reviewed in this report. Cancer can therefore be described as the result of a multistep process and as a multifactorial disease; this view not only helps in understanding the molecular and cellular mechanisms of carcinogenesis, but offers a framework to interpret the results of observational studies which suggest an 'interaction' between different risk factors.

1. Biological interaction

Although the precise role played at the molecular and cellular level by known carcinogens is in most cases unknown, it is plausible that certain carcinogens, in particular those consisting of complex mixtures such as tobacco smoke, act on more than one step of the carcinogenesis pathway. This is consistent with the epidemiological evidence of tobacco acting both as an 'early-stage' (e.g., as a mutagen) and a 'late-stage' (e.g., as a promoter) carcinogen (Tubiana, 1999, Hazelton et al., 2005).

A practical consequence of the multifactorial nature of cancer and of interactions between carcinogens is that the same cases of cancer can be attributed to more than one risk factor. This notion has far-reaching implications in the interpretation of estimates of attributable cancers such as those presented in this report. First, we should aim at identifying risk factors that explain more than 100% of a specific cancer when their individual effects are summed. Second, any estimate of the 'global' burden of cancer attributable to multiple causes should take into account the overlap between the effects of different carcinogens. As a consequence, for a specific cancer, the attributable fraction for all risk factors considered together should be smaller than the mere sum of the AFs associated with each risk factor.

The independence of the effects of risk factors, leading to multiplicative effects of relative risks, as outlined in Table C2.1, is the default assumption in most calculations of attributable fractions. It is based on the hypothesis that different risk factors act on different carcinogenic pathways. This choice is justified by the lack of detailed quantitative data on the risks resulting from combined exposure to several risk factors. Indeed, the statistical power needed to demonstrate an interaction is lacking in the vast majority of epidemiological studies. The hypothesis of the multiplicative effect of relative risks can be considered as reasonable since it has already been described at least for the two main risk factors, tobacco smoking and alcohol drinking, as risk factors for laryngeal cancer (Figure C2.1). This multiplicative effect has been further confirmed in relative risk models (Roy and Estève, 1998). However, a model with less than multiplicative interaction seems to best fit the data on combined exposure to asbestos and tobacco smoke with respect to lung cancer risk (Vainio and Boffetta, 1994).

A detailed quantitative review of all combinations of risk factors goes beyond the scope of this report, but the reader should be aware of the following conclusions:

a) the number of attributable cancers due to a combination of risk factors is less than the sum of the number attributable to each of the risk factors;

b) prevention of the same cancers can take place through multiple interventions; in other

words, prevention of one cause of cancer may also reduce the number of cancers due to another cause;

c) estimates of attributable cancers adding up to a total of 100% are not biologically or statistically correct.

2. Interaction between risk factors considering independence of risk factors

Although the available epidemiological data support the notion of interaction between risk factors, in most instances they fall short of conclusively demonstrating its precise nature. To assess the importance of interactions for AFs of cancer, we estimated the AF for the combination of exposures under the hypothesis of independent exposures and effect. This hypothesis implies the multiplication of relative risks in the case of combined exposures. For two risk factors, A and B, the AF of exposure to either factor is given by:

$$AF = \frac{p_A p_B (RR_A RR_B - 1) + p_A (1 - p_B)(RR_A - 1) + p_B (1 - p_A)(RR_B - 1)}{p_A p_B (RR_A RR_B - 1) + p_A (1 - p_B)(RR_A - 1) + p_B (1 - p_A)(RR_B - 1) + 1}$$

where P_A and P_B are the prevalences of exposure to factors A and B, and RR_A and RR_B are the corresponding relative risks. This formula can be written as:

$$AF = AF_A + AF_B - (AF_A \times AF_B)$$

This formula can be generalized to more than two risk factors. This approach allowed us to estimate the fraction attributable to established risk factors for all cancers in 2000.

We calculated the combined AF for selected risk factor–cancer mortality associations in men and women (Tables C2.2 and C2.3), as well as in both sexes combined (Table C2.4). These tables show that, in the case of a risk factor with high relative risk, the contribution of additional risk factors to the combined AF is small. For instance, for lung cancer in men, the AF is 83% for tobacco only, and adding the effect of occupation and pollutants only increases the overall percentage of lung cancer attributed to one of these causes to 85%. However, given the uncertainties in current knowledge of the biological

interactions between different cancer risk factors, the figures presented in Tables C2.2–C2.4 should be interpreted with caution.

References

Hanahan D, Weinberg RA. The hallmarks of cancer. Cell 2000;100:57–70.

Hazelton WD, Clements MS, Moolgavkar SH. Multistage carcinogenesis and lung cancer mortality in three cohorts. Cancer Epidemiol Biomarkers Prev 2005;14:1171–1181.

Roy P, Estève J. Using relative risk models for estimating synergy between two risk factors. Stat Med 1998;17:1357–1373.

Tubiana M. Contribution of human data to the analysis of human carcinogenesis. Comptes Rendus Acad Sc, Sciences de la vie / Life sciences 1999;322:215-224.

Tuyns A, Estève J, Raymond L, et al. Cancer of the lartnx/hypopharynx, tobacco and alcohol : IARC international case-control study in Turin and Varese (Italy), Zaragosa and Navarra (Spain), Geneva (Switzerland) and Calvados (France). Int J Cancer 1988; 41: 483-491.

Vainio H, Boffetta P. Mechanisms of the combined effect of asbestos and smoking in the etiology of lung cancer. Scand J Work Environ Health. 1994;20:235–242.

Table C2.1–Interaction between two risk factors A and B

		Risk factor A	
		–	+
Risk factor B	–	RR=1	RR_A
	+	RR_B	RR_{AB}

– Multiplicative model of interaction: $RR_{AB} = RR_A \times RR_B$
– Presence of positive interaction: $RR_{AB} > RR_A \times RR_B$

Table C2.2. Summary of attributable fractions of cancer deaths (%) and estimate of the overall attributable fraction to an established risk factor by cancer site for men in France in 2000

Cancer site	Tobacco	Alcohol	Infection	Obesity and overweight	Inactivity	UV light	Occupation	Pollutants	Total
Bladder	52.8						5.1		55.2
Central nervous system									0.0
Colon-rectum		11.2		6.6	5.1				21.3
Gallbladder									0.0
Hodgkin lymphoma			40.0						40.0
Kidney	26.4			14.6					37.2
Larynx	75.9	57.3					3.1		90.0
Leukaemia							4.1		4.1
Liver	37.5	31.8	32.4						71.2
Lung	83.0						11.3	0.4	85.0
Melanoma						71.1			71.1
Mesothelioma							83.2	2.4	83.6
Multiple myeloma									0.0
Non-Hodgkin lymphoma			8.0						8.0
Oesophagus	51.1	55.2		5.0					79.2
Oral cavity and pharynx	71.5	70.7	6.7						92.2
Pancreas	24.9								24.9
Prostate									0.0
Sinonasal							27.0		27.0
Stomach	31.1		18.1						43.6
Thyroid									0.0
All cancer	33.4	9.4	3.1	1.1	0.5	0.6	3.7	0.1	42.5

The total for each cancer represents the overall percentage of cancers attributed to an established risk factor

Table C2.3. Summary of attributable fractions of cancer deaths (%) and estimate of the overall attributable fraction to an established risk factor by cancer sites for women in France in 2000 *

Cancer site	Tobacco	Alcohol	Infection	Obesity and overweight	Inactivity	UV light	HRT-OC	Occupation	Pollutants	Total
Bladder	39.3							0.6		39.6
Breast		9.4		4.8	10.1		10.7			30.8
Central nervous system										0.0
Cervix uteri*	22.9		100							100.0
Colon-rectum		2.7		4.9	9.2					16.0
Corpus uteri				17.8						17.8
Gallbladder										0.0
Hodgkin lymphoma			40.0							40.0
Kidney	11.5			11.3						21.5
Larynx	64.8	17.8						0.3		71.2
Leukaemia								0.4		0.4
Liver	17.1	8.4	25.1							43.1
Lung	69.2							4.5	3.8	71.7

Table C2.3. cont'd - Summary of attributable fractions of cancer deaths (%) and estimate of the overall attributable fraction to an established risk factor by cancer sites for women in France in 2000 *

Cancer site	Tobacco	Alcohol	Infection	Obesity and overweight	Inactivity	UV light	HRT-OC	Occupation	Pollutants	Total
Melanoma						71.1				71.1
Mesothelioma								38.4	2.4	39.9
Multiple myeloma										0.0
Non-Hodgkin lymphoma			8.0							8.0
Oesophagus	34.4	16.9		7.3						49.4
Oral cavity and pharynx	28.5	24.6	6.7							49.7
Ovary							1.9			1.9
Pancreas	17.0									17.0
Sinonasal								6.5		6.5
Stomach	14.3		18.1							29.9
Thyroid										0.0
All cancer	9.6	3.0	4.4	2.3	3.2	0.8	2.2	0.5	0.3	23.6

The total for each cancer represents the overall percentage of cancers attributed to an established risk factor
HRT-OC: Hormone replacement therapy and oral contraceptive use
* For cervix uteri all cancers are attributed to infection

Table C2.4. Summary of attributable fractions of cancer deaths (%) and estimate of the overall attributable fraction to an established risk factor by cancer sites for both sexes combined in France in 2000 *

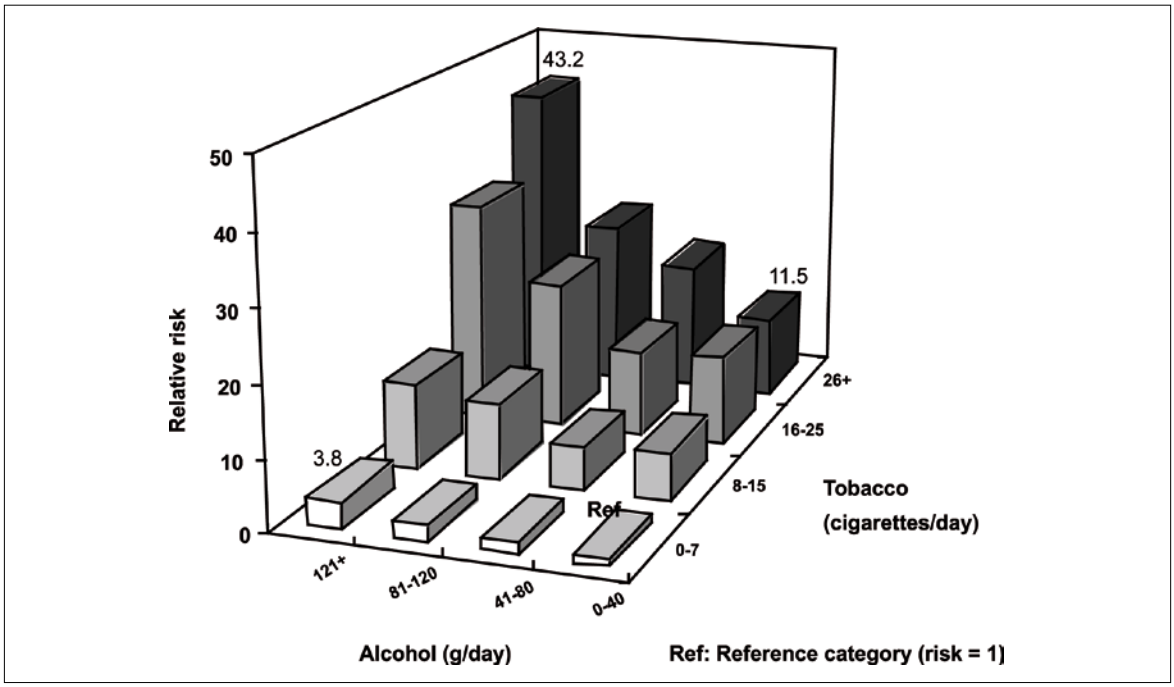
Cancer site	Tobacco	Alcohol	Infection	Obesity and overweight	Inactivity	UV light	HRT-OC	Occupation	Pollutants	Total
Bladder	49.6							4.0		51.6
Breast		9.4		4.8	10.1		10.7			30.8
Central nervous system										0.0
Cervix uteri*	22.9		100.0							100.0
Colon-rectum		7.2		5.8	7.1					18.7
Corpus uteri				17.8						17.8
Gallbladder										0.0
Hodgkin lymphoma			40.0							40.0
Kidney	20.9			13.4						31.5
Larynx	75.0	54.1						2.9		88.8
Leukaemia								2.3		2.3
Liver	32.6	26.1	30.6							65.5
Lung	80.6							10.1	1.0	82.8

Table C2.4. cont'd - Summary of attributable fractions of cancer deaths (%) and estimate of the overall attributable fraction to an established risk factor by cancer sites for both sex in France in 2000 *

Cancer site	Tobacco	Alcohol	Infection	Obesity and overweight	Inactivity	UV light	HRT-OC	Occupation	Pollutants	Total
Melanoma						71.1				71.1
Mesothelioma								73.8	2.4	74.4
Multiple myeloma										0.0
Non-Hodgkin lymphoma			8.0							8.0
Oesophagus	48.3	48.8		5.3						74.9
Oral cavity and pharynx	64.7	63.4	6.7							88.0
Ovary							1.9			1.9
Pancreas	21.2									21.2
Prostate										0.0
Sinonasal								20.9		20.9
Stomach	24.6		18.1							38.2
Thyroid										0.0
All cancer	23.9	6.9	3.6	1.6	1.6	0.7	0.9	2.4	0.2	35.2

The total for each cancer represents the overall percentage of cancers attributed to an established risk factor
HRT-OC: Hormone replacement therapy and oral contraceptive use
* For cervix uteri all cancers are attributed to infection

Figure C2.1 - Relative risk of laryngeal cancer for tobacco smoking and alcohol drinking in a study from Southern Europe (Tuyns et al., 1988)



Risk factors for which no estimates were calculated

Section D1: Ionizing radiation

1. The low-dose-effect relationship controversy

Most of the dose from ionizing radiation received by human beings originates from medical X-rays and background radiation. The term "background radiation" encompasses cosmic radiation and terrestrial radiation, including radon decay products. Terrestrial radiation comes mainly from naturally radioactive atoms present in the earth's surface (e.g., uranium, thorium and their decay products) that can irradiate living beings through close contact, ingestion of water and foodstuffs and inhalation of air containing radionuclides or may be incorporated into the body (e.g., potassium 40, carbon 14 and tritium). There are major geographical variations in cosmic and terrestrial radiation: doses due to cosmic radiation are higher in polar regions and at altitude, and terrestrial radiation depends on concentrations of naturally radioactive atoms that vary greatly between different geological structures (Billon et al., 2005). However, the radiation dose due to radionuclides incorporated into the body is constant across the world, because their uptake is regulated by homeostatic mechanisms. The average annual effective dose delivered by background irradiation including radon is 2.4 mSv, with a typical range between 1 and 10 mSv in most countries, although in some regions it can reach 50 to 80 mSv (UNSCEAR 2000). Most of the effective dose, however, is related to lung dose from radon and its decay products; the average effective dose[1] excluding radon is of the order of 1 mSv.

Most of these sources deliver relatively low doses of less than 20 mSv per year at very low dose rates, i.e. below 2.5 µSv per hour. Most people in France have an average annual exposure below 5 mSv per year from all three sources (natural, medical and industrial). A small fraction of the total population is or may be exposed to higher doses of ionizing radiation for professional (e.g., pilots and aircrews, radiation workers in industry, research or medicine), circumstantial (e.g., high terrestrial content in radioactive products) or medical reasons (e.g., radiotherapy for cancerous diseases).

The old unit of radioactivity is the curie, the more recent one is the becquerel, which is much smaller. The amount of energy deposited in tissue by an exposure to ionizing radiation ("a dose") can be expressed in joules per kilogram. The International Commission on Radiological Units gives 1 joule per kilogram a special name, the gray. However, simply measuring the amount of energy absorbed by tissue from ionizing radiation is not enough to predict the amount of potential harm. There are different kinds of ionizing radiation, such as alpha, beta and gamma rays and neutrons. Experience has shown that a 1-gray dose of alpha rays, for example, is about 10 to 20 times more harmful than a 1-gray dose of gamma rays. Beta rays and X-rays are about as harmful as gamma rays. The relative biological efficiency (RBE) of neutrons versus gamma rays varies inversely with neutron energy down to 0.4 MeV, where it can reach values of 20 and more. To express the size of an exposure in terms of potential harm, a measurement of the absorbed dose in joules per kilogram (hence in grays) in a given organ or tissue is multiplied by "quality factors" for that kind of radiation. The quality factors are chosen so that 1 sievert of radiation is the amount of any kind of radiation which would cause the same amount of harm as would result from absorbing 1 gray of X-rays in the same organ or tissue; in this case the sievert is said to measure "dose equivalent'. The quality factor has been in part determined experimentally (RBE) and in part based on expert judgement. This dimensionless quality factor is chosen by the International Commission for Radiation Protection and the International Commission of Radiological Units. Some authors still use old units. One gray is equal to 100 rad and one sievert to 100 rem.

While the carcinogenic effects of high- and medium-dose radiation are well established, there is much controversy about the carcinogenic effects of low doses (10 to 100 mSv) of ionizing radiation in humans and even more so for very low doses (<10 mSv). This controversy has considerable public health implications, since most human beings are exposed to low or very low doses of ionizing radiation. Even if low-dose radiation entailed very low cancer risk, the proportion of cancer attributable to these sources of radiation might be substantial because everybody is exposed to cosmic, terrestrial and medical radiation. Therefore, a small error in low-dose risk assessment leads to large errors in the number of cancers attributed to ionizing radiation exposures, whether occupational or residential.

Estimation of low-dose risk critically depends on our ability to establish the relationship between dose (and the dose-delivery pattern, e.g., acute or fractionated, protracted) and detrimental effects, in particular within the range of low and very low doses.

A detailed discussion of this controversy is beyond the scope of this report and readers should refer to relevant publications (Rossi and Kellerer, 1972; Tubiana et al., 2004, 2005a, b, 2006a, b; Simmons, 2004; Brenner and Hall, 2003b, 2004; Brenner and Sachs, 2006; US NRC, 2007), but the different positions are summarized below.

There is a consensus based on recent results of biological and animal experimentation that:

- defence against ionizing radiation involves not only cells but their microenvironment and the immunological system ;
- changes in cell signalling and gene transcription (either activation or inhibition) are not the same in response to very low (< 10 mSv), low (< 100 mSv) or higher doses;
- when only a small proportion of cells are damaged, elimination by death is the main cell and tissue response (Rothman, 2003; Collis, 2004).

The position of the International Commission on Radiological Protection (ICRP), the Biological Effects of Ionizing Radiation committee (BEIR VII) is that:

- most of these results were obtained in vitro and have not been confirmed in vivo,
- the initial biophysical cell damage by ionizing radiation is proportional to the dose,
- a cancer arises from transformation of a single cell and cell neoplastic transformation can be induced by a bystander effect or result in genetic instability which could involve a supra-linear low-dose–effect relationship;
- hence, even the lowest dose has the potential to cause a small increase in the risk of cancer; the magnitude of the effect, however, is uncertain and the risk may be lower or higher than that predicted by a linear no-threshold (LNT) model;
- an LNT dose–effect relationship is compatible with epidemiological data and remains the best dose–effect model;
- an LNT dose–effect relationship allows the estimation of cancers attributable to ionizing radiation, whatever the dose, with adjustments taking into account the dose rate;
- any additional dose one receives, be it very low, must be added to doses we receive from other, unavoidable sources, including natural background radiation. On the basis of a lifetime commitment to dose from ionizing radiation (i.e., tens of mSv), we are above any threshold that might be credible from a radiobiological or even epidemiological perspective.

Conversely, the French academies of medicine and science consider that:

Because many organs and tissues of a human being are more or less exposed selectively as a result of internal contamination and localized medical exposures, it is convenient to use an additional concept, that of “effective dose”, which characterizes the overall potential health risk caused by any combination of heterogeneously distributed radiation. The effective dose accounts both for absorbed energy and type of radiation and for susceptibility of various organs and tissues to development of a radiation-induced cancer. This is done using a specific weighting factor for each tissue or organ on the basis of an equivalence of this risk compared to the risk resulting from the same dose equivalent homogeneously delivered to the entire body. The sum of these weighting factors is equal to unity. The sievert is also used as the unit for effective dose.

- multiple and convergent data show that not one single but several strategies provide cell and tissue defence against ionizing radiation;

- these are more effective for low doses and at low dose rates, since in that dose range cell death is predominant. DNA repair (which can be error-prone) is mainly activated against higher doses, in order to preserve tissue function; moreover, elimination of damaged or mutated cells is more effective at low doses and low dose rates (low dose hypersensitivity). Mitotic death eliminates cells with DNA damage when the dose or dose rate is too low to trigger activation of DNA repair.

- the incidence of misrepair is higher at high doses and high dose rates. Adaptive response can increase the efficacy of cell defence. Carcinogenic effect (per dose unit) varies with dose and dose rate.

- the LNT dose–effect relationship is incompatible with some biological data and with data pertaining to cancer induction by alpha emitters;

- for reasons of statistical power, most epidemiological studies amalgamate high-and low-dose exposure data and postulate an LNT dose–effect relationship. This is based on the erroneous hypothesis that cancer induction by radiation and defence mechanisms are similar in both cases ;

- the preliminary meta-analysis of cohort studies for which low-dose data (< 100 mSv) were available show no significant risk excess, either for solid cancer or for leukaemias;

- an LNT dose–effect relationship allows estimation of cancer attributable to ionizing radiation doses of 100–200 mSv, but leads to overestimation for lower doses.

Observational epidemiological studies on workers or patients will probably never have the statistical power to demonstrate a modest increased cancer risk associated with low-dose radiation (e.g., less than 10% excess risk), as such studies would need to include millions of subjects followed up over long periods, with accurate measurements of radiation exposure and appropriate control of numerous potential confounding factors (e.g., smoking, socioeconomic status).

Comparisons of mortality rates between groups deemed to be more highly exposed to radiation and the general population or some adequate control group have often led to the finding of equivalent or lower all-cause death and cancer death rates in the exposed groups. The current explanation for this observation is the so-called “healthy worker effect”, which assumes that subjects professionally exposed to radiation have higher socioeconomic status and probably have healthier lifestyle than average and therefore their cancer risk is lower than that of the average population. (Doll et al., 2005; Cameron 2002; Daunt 2002; Muirhead et al., 1999, 2003). This concept has been criticized and evidence for less smoking and/or drinking among workers has yet to be provided.

Assessment of cancer risk associated with exposure to low doses of ionizing radiation often relies upon model approaches, mainly using logistic models that allow other risk factors, such as tobacco or alcohol consumption, to be taken into account. Most models are based on assumptions about the type of relationship between low-dose radiation and organ-specific cancer risk. The US Committee on the Biological Effects of Ionizing Radiation (BEIR) family model (health risks from exposure to low levels of ionizing radiation) is often used for estimating excess risk of cancer due to low-dose radiation. The BEIR VII report issued in 2006 (BEIR VII 2006) includes the most recent version of this model. The model is based on the LNT hypothesis which postulates that the carcinogenic effect per unit dose is constant, irrespective of the dose and the dose rate. The validity of this assumption has been challenged by the report of the French academies (Tubiana, 2005) which provided biological and epidemiological arguments against this constancy (see above).

An alternative approach is to avoid the use of any model and to estimate the radiation odds-ratios for different dose ranges, taking into account potential confounding factors. This approach can also take into account the fact that the mechanisms of defence against ionizing radiation are not the same for different doses.

Because of the debate surrounding the effects of low doses of radiation, we chose not to estimate the numbers of cancer attributable to ionizing radiation in France, but rather to review briefly issues related to cancer risk and low-dose radiation,

including radon exposure and the consequences of the Chernobyl accident and its impact on thyroid cancer incidence.

2. Exposure in France to ionizing radiation

Background radiation

In France, according to the Institut de Radioprotection et de Sûreté Nucléaire (IRSN 2002), cosmic and terrestrial radiation delivers an average annual dose of 2.4 mSv. According to the BEIR VII model (2006), such exposure could cause nearly 6% of all cancers. However, large studies devoted to natural background exposures have not revealed any increased risk, even for doses 30 times higher. Thus, the existence of a background radiation cancer risk in France is speculative and no reliable attributable fraction can be proposed.

Indoor radon exposure

Release of radon and its decay products from the ground or from building materials results in indoor exposure. Exposure levels in houses are typically one order of magnitude lower than in underground mines. The estimation of an attributable risk due to indoor radon exposure requires dosimetric estimates and relative risk (RR) assessments for low radon concentrations.

The level of exposure of the French population to radon is not known precisely. Radon measurement requires caution and radon levels are highly sensitive to geology, season, weather, type of dwelling (private house or apartment building), construction materials and floor. Surveys carried out in France in 1982–2000, including 12 641 measurements (IRSN database) showed a crude arithmetic mean of 89 Bq/m3 and a geometric mean of 54 Bq/m3 for the entire French population. Weighted for population density, the average was 68 Bq/m3 (Billon et al., 2003). Though the geometric mean of these measurements is close to the weighted average of measurements in 29 European countries (58 Bq/m3) (UNSCEAR, 2000), the latter data are not representative of French population exposure, due to overrepresentation of individual dwellings and ground-floor measurements. These values contrast with those estimated by the Observatoire de la Qualité de l'Air Intérieur (OQAI) (Kirchner et al., 2006) including 570 houses representative of 24 million dwellings in continental metropolitan France: median 31 Bq/m3 in bedrooms and 33 Bq/m3 in other rooms.

A pooled analysis of European studies of residential radon exposure and lung cancer resulted in an RR of 1.08 (95% CI 1.03–1.16) for an increase in radon exposure of 100 Bq/m3 (Darby et al., 2005). The relative risk excess is, however, not significant for radon concentrations lower than 100 Bq/m3.

Range (Bq/m3)	RR	95% CI
< 25	1.00	0.87–1.15
25–49	1.06	0.98–1.15
50–99	1.03	0.96–1.10
100–199	1.20	1.08–1.32
200–399	1.18	0.99–1.42
400–799	1.43	1.06–1.92

These estimates take into account tobacco consumption level, but neither its duration nor environmental tobacco smoke. None of the relevant tobacco risk parameters *("daily amount smoked, duration of smoking, age at onset of smoking, cumulative amount smoked […], environmental tobacco smoke"[2])* were taken into account in the quoted studies of radon risk (Lubin, 1997; Darby et al., 2005).

Consequences of radon exposure increase dramatically for smokers: *"In the absence of other causes of death, the absolute risks of lung cancer by age 75 years at usual radon concentrations of 0, 100, and 400 Bq/m3 would be about 0.4%, 0.5%, and 0.7%, respectively, for lifelong non-smokers, and about 25 times greater (10%, 12%, and 16%) for cigarette smokers."* (Darby et al., 2005).

The calculation of attributable fraction for radon exposure is therefore debatable, since it can rely either on significant proven risk (smokers and significant RR dose range) or on hypothetical extrapolated RR (including non-smokers and using global dose–RR estimates).

An estimate of lung cancer deaths in France attributable to indoor radon exposure (Catelinois et al., 2006) ranges from 1234 (90% uncertainty interval,

[2] Giles G, Boyle P. Smoking and lung cancer. In : Tobacco, Boyle P, et al. Ed., Oxford University Press, 2004; pp. 492-493.

593–2156) to 2913 (90% UI, 2763–3221), depending on the model considered. This estimate used an LNT dose–risk model which results in a high proportion of deaths (47%) related to radon concentration in the range 0–99 Bq/m3.

These results are debatable because of several considerations that lead to overestimation of the burden due to radon:

- epidemiological and animal data show a dose–risk relationship threshold for alpha emitters which should be taken into account;
- no significant risk excess was demonstrated for indoor radon exposure in the 0–99 Bq/m3 concentration range (Darby et al., 2005);
- Catelinois et al. made use of IRSN estimates of the French population exposition to radon (adjusted mean 87 Bq/m3) which are not consistent for French dwellings. Kirchner (2006) estimated that levels are significantly lower (31–33 Bq/m3) and that radon concentrations are higher than 100 Bq/m3 in only about 11% of dwellings, compared with 24% according to IRSN.

Medical radiation

Medical radiation includes diagnostic and therapeutic procedures with X-rays, scintigrams and metabolic radiotherapy (making use of radioactive products). Average doses and total annual doses resulting from diagnostic procedures were calculated for the year 2002 according to two hypotheses (Scanff, 2005). The main results (average of low and high hypothesis estimates) are given in the following table[1].

	Number of acts (%)	**Collective effective dose in man - mSv (%)**	**Average effective dose per act mSv**
Conventional radiology	60 635 575 (89.8%)	16 684 755 (36.6%)	0.28
Computerized tomography	5 109 481 (7.5%)	17 682 526 (38.8%)	3.46
Nuclear medicine	849 620 (1.2%)	3 402 402 (7.4%)	4.00
Interventional radiology	892 385 (1.3%)	7 771 511 (17%)	8.71
Total	67 487 062 (100%)	45 541 194 (100%)	0.67

The average dose per French inhabitant was 0.75 mSv/y. Estimates for 1982 from UNSCEAR (1988) lead to an average effective dose of 1.6 mSv/y, if one redistributes among all French subjects a “collective dose” estimated for each anatomic site of radiographic examination. These site-specific “collective doses” are displayed in the following table :

Collective effective dose equivalent from diagnostic x-ray examinations in France, 1982

a/ Examinations in which fluoroscopy is only used for positioning the patient prior to film radiography.

Examination	Collective effective dose equivalent (man Sv)	Accounted for by fluoroscopie (%)
Cervical spine	1680	18a/
Thoracic spine	2100	16.5 a/
Lumbar spine	8500	13 a/
Sacro-lumbar spine	3400	7 a/
Pelvis, hip	5350	3 a/
Abdomen	4120	6.5 a/
IV urography	20580	11.5 a/
Hysterography	810	17
Cholecystography	4860	34.5
Skull	4990	10 a/
Barium enema	8210	21.5
Barium meal	7460	31.5
Thorax	4110	3 a/
Cerebral angiography	1780	15
Thoracic angiogaphy	680	70.5
Abdominal angiography	5590	34
Inferior limbs angiography	280	15
Phlebography	940	37
Obstetrical abdomen	930	8 a/
Pyelography	370	24

An attributable fraction of cancers calculated from these exposures based on the collective dose of 45 541 194 man Sv is not reliable, since procedures generally involve very low doses for which the levels

of risk are unknown and cannot be merely derived from high-dose data. For example, each of the 5 to 6 million chest radiographic examinations delivers a mean effective dose of 0.02 mSv; each of the 1.5 to 2.2 million head CT scans delivers about 1.8 mSv.

An attributable fraction of cancers could be calculated relying on individual dosimetry estimates for repeated examinations resulting in total doses high enough for reliable risk factors to be available (> 50–100 mSv). Such cases are infrequent, however, and the required data are not available. Moreover, a study conducted in 2001–3 showed that for a given procedure, the dose varies greatly according to the radiographic device. For example, a face + profile chest radiography results in doses ranging from 0.09 to 0.70 mGy, and a profile lumbar column radiography from 9.5 to 36 mGy. Dosimetric estimation derived from the number and type of examinations, without actual dosimetric measurements, is therefore very approximate.

Computations using the BEIR VII model taking into account the age-distribution of medical X-ray examinations performed in the United Kingdom (Berrington et al., 2004) are a subject of controversy (Tubiana et al., 2004).

It may be noted that about twice as many medical X-ray examinations are performed in France as in the United Kingdom, and effective doses for medical X-rays in France are among the highest in industrialized countries (UNSCEAR 2000; Donadieu et al., 2006).

3. Impact of fallout from the Chernobyl accident on cancer in France

The Chernobyl accident occurred on 26 April 1986. Most of central and western Europe received fallout from the accident, with geographical variations in levels, depending on winds and other atmospheric conditions that prevailed in the days after the accident.

International collaborative studies coordinated by IARC and WHO have produced two reports on cancer consequences of the Chernobyl accident, for local populations and for the whole of Europe (Cardis et al., 2006a, b).

Estimation of cancers that could be attributable to fallout, based on food contamination measurements carried out in 1986 by the Service Central de Protection contre les Rayonnements Ionisants (SCPRI), indicated 0.5 to 22 attributable cancers for the whole period 1991–2000 (Verger et al., 2000, 2003). These results are probably biased towards overestimation, since measurements showing no food contamination were discarded. The authors used an LNT relationship but recognized that this model may overestimate the risk.

According to the BEIR VII model, between 0.003 and 0.012% of all cancers occurring before the age of 75 years (i.e., between 8 and 33 cancers) would be attributable to Chernobyl fallout in France in 2000. However, the validity of this model is open to discussion (see above).

Modelling performed by Catelinois et al. (2005) for eastern France, where the level of fallout was higher, indicated that during 1991–2007, out of 894 to 1716 thyroid cancers in subjects below 15 years of age, the excess due to fallout could be between 5 and 63 cases.

These estimates of attributable cancer rely on debatable dose reconstructions and dose–risk relationships. So far, direct epidemiological evidence of an excess in thyroid cancer incidence in France due to fallout is not available, but it should be noted that the power to detect an increase of the order of that predicted by the BEIR VII model is very small.

A sustained increase in thyroid cancer incidence was observed over recent decades (mainly for papillary cancer, little for follicular cancer), with no change in slope of the incidence curve after 1986 (Figure D.1). In contrast, mortality rates from thyroid cancer remain low and steadily decrease with the calendar year, without any noticeable influence of the Chernobyl accident (Figure D.2). The increase in thyroid cancer incidence in France over recent decades is mostly due to the introduction of new diagnostic procedures; a study of diagnostic practices in six centres specializing in thyroid diseases in France by Leenhardt et al. (2004 a,b) showed the following data on methods used for thyroid investigation:

	1980	2000
Ultrasonography	3%	85%
Fine needle biopsy	4.5%	23%

Since thyroid glands (particularly in women) often harbour a few islets of “cancerous” tissues, the more imaging and biopsy methods gain in sensitivity,

the more “thyroid cancers” are found. The clinical significance of most screen-detected thyroid cancers remains questionable because most would remain indolent and would never progress to an invasive cancer.

Increases in thyroid cancer incidence in departments with cancer registries (Colonna et al., 2002) showed no correlation between the magnitude of the annual increase in thyroid incidence and estimates of deposition of caesium 137 or iodine 131 in France in April and May 1986.

In April 2006, the InVS released complete reports on surveillance of thyroid cancer in France, including numerous new data showing that the Chernobyl accident is not likely to have contributed to increasing the incidence and mortality from thyroid cancer in France (Chérié-Challine et al., 2006a,b)[3].

4. Concluding remarks

At present, no direct observational epidemiological data support an association between exposure to low doses of ionizing radiation and cancer occurrence. Hence, observational epidemiological data, which are also compatible with absence of association or with a rather small association, are very difficult to assess. Estimates based on LNT models, on the other hand, may markedly overestimate radiation-attributable cancers.

References

BEIR VII. Health Risks from Exposure to Low Levels of Ionizing Radiation: BEIR VII Phase 2. National Academy Press, 2006, 424p

Berrington de Gonzalez A, Darby S. Risk of cancer from diagnostic X-rays: estimates for the UK and 14 other countries. Lancet 2004;363:345–351.

Billon S, Morin A,Caër S, et al. Evaluation de l’exposition à la radioactivité naturelle en France. SFRP Montpellier 2003. http://www.sfrp.asso.fr/Montpellier2003/pdf/billon.pdf

Billon S, Morin A, Caër S, et al. French population exposure to radon, terrestrial gamma and cosmic rays. Radiat Prot Dosimetry 2005;113:314–320.

Brenner DJ, Hall EJ. Morality patterns in British and US radiologists: what can we really conclude? Br J Radiol 2003;76:1–2.

Brenner DJ, Hall EJ. Risk of cancer from diagnostic X-rays. Lancet 2004;363:2192.

Brenner DJ, Sachs RK. Estimating radiation-induced cancer risks at very low doses: rationale for using a linear no-threshold approach. Radiat Environ Biophys 2006;44:253–256.

Cameron JR. Radiation increased the longevity of British radiologists. Br J Radiol 2002;75:637–639.

Cardis E, Krewski D, Boniol M, et al. Estimates of the cancer burden in Europe from radioactive fallout from the Chernobyl accident. Int J Cancer 2006;119:1224-1235.

Cardis E, Howe G, Ron E, et al. Cancer consequences of the Chernobyl accident: 20 years after. J Radiol Prot 2006; 26:125–137.

Catelinois O, Laurier D, Verger P, et al. Uncertainty and sensitivity analysis in assessment of the thyroid cancer risk related to Chernobyl fallout in Eastern France. Risk Analysis 2005;25:243–254.

Catelinois O, Rogel A. Laurier D, et al. Lung cancer attributable to indoor radon exposure in France: impact of the risk models and uncertainty analysis. Environ Health Perspect 2006;114;1361–1366.

Chérié-Challine L et les membres du Comité de Rédaction. Surveillance sanitaire en France en lien avec l’accident de Tchernobyl. Synthèse du Rapport INVs, Saint-Maurice, 2006 (www.invs.sante.fr).

Chérié-Challine L et les membres du Comité de Rédaction. Surveillance sanitaire en France en lien avec l’accident de Tchernobyl. Bilan actualisé sur les cancers thyroïdiens et études épidémiologiques en cours en 2006, Saint-Maurice, 2006 (www.invs.sante.fr)

Collis SJ, Schwaninger JM, Ntambi AJ. et al. Evasion of early cellular response mechanisms following low level radiation induced DNA damage. J Biol Chem 2004;279:49624–49632

Colonna M, Grosclaude P, Remontet L, et al. Incidence of thyroid cancer in adults recorded by French cancer registries (1978–1997). Eur J Cancer 2002;38:1762–1768.

Darby S, Hill D, Auvinen A, et al. Radon in homes and risk of lung cancer: collaborative analysis of individual data from 13 European case-control studies. BMJ 2005;330:223.

Daunt N. Decreased cancer mortality of British radiologists. Br J Radiol 2002;75:637–639.

Doll R, Berrington A, Darby SC. Low mortality of British radiologists. Br J Radiol 2005;78:1057–1058.

[3] Available at www.invs.sante.fr

Donadieu J, Scanff P, Pirard P, Aubert B. Exposition médicale aux rayonnements ionisants à visée diagnostique de la population française: état des lieux fin 2002 en vue de la mise en place d'un système de surveillance. Bull Epid Hygiène 2006;15–16:102–106.

IRSN. Exposition médicale de la population française aux rayonnements ionisants: Etat des lieux fin 2002 Rapport établi à partir des données disponibles fin 2004.

IRSN. Le radon. http://www.irsn.net/vf/05_inf/05_inf_1dossiers/05_inf_16_radon/05_inf_16_0radon.shtm

Kirchner S, Arenes JF, Cochet C, et al. Observatoire de la Qualité de l'Air Intérieur. Campagne naationale logements: état de la qualité de l'air dans les logements français. Rapport final. Centre Scientifique et Technique du Bâtiment 2006.

Leenhardt L, Bernier MO, Boin-Pineau MH, et al. Advances in diagnostic practices affect thyroid cancer incidence in France. Eur J Endocrinol 2004;150:133–139

Leenhardt L, Grosclaude P, Chérié-Challine L; Thyroid Cancer Committee. Increased incidence of thyroid carcinoma in France: a true epidemic or thyroid nodule management effects? Report from the French Thyroid Cancer Committee. Thyroid 2004;14:1056-1060.

Muirhead CR, Goodill AA, Haylock RG, et al. Occupational radiation exposure and mortality: second analysis of the National Registry for Radiation Workers. J Radiol Prot 1999;19:3–26.

Muirhead CR, Bingham D, Haylock RG, et al. Follow up of mortality and incidence of cancer 1952-98 in men from the UK who participated in the UK's atmospheric nuclear weapon tests and experimental programmes. Occup Environ Med 2003;60:165–172.

Remontet L, Esteve J, Bouvier AM, et al. Cancer incidence and mortality in France over the period 1978-2000. Rev Epidemiol Sante Publique 2003;51:3-30.

Rossi HH, Kellerer AM Radiation carcinogenesis at low doses. Science 1972;175:200–202.

Rothkamm K, Löbrich M. Evidence for a lack of DNA double-strand break repair in human cells exposed to very low x-ray doses. Proc Natl Acad Sci USA 2003;100:5057–5062.

Scanff P, Donadieu J, Pirard P, Aubert B. Exposition médicale de la population française aux rayonnements ionisants. Rapport IRSN-InVS, 2005.

Simmons JA. Risk of cancer from diagnostic X-rays. Lancet 2004;363:1908–1909; author reply 1910.

Tubiana M, Aurengo A, Masse R, Valleron AJ. Risk of cancer from diagnostic X-rays. Lancet 2004; 363:1908.

Tubiana M, Aurengo A, Averbeck D, et al. Dose–effect relationships and estimation of the carcinogenic effects of low doses of ionizing radiation. Paris, Institut de France, Académie des Sciences, 2005a (www.academie-sciences.fr/publications/ rapports/pdf/dose_effet_07_04_05_gb.pdf)

Tubiana M. Dose-effect relationship and estimation of the carcinogenic effects of low doses of ionizing radiation: the joint report of the Académie des Sciences (Paris) and of the Académie Nationale de Medecine. Int J Radiat Oncol Biol Phys 2005b;63:317–319.

Tubiana M, Aurengo A, Averbeck D, Masse R. The debate on the use of linear no threshold for assessing the effects of low doses. J Radiol Prot 2006a;26:317–324.

Tubiana M, Aurengo A, Averbeck D, Masse R. Recent reports on the effect of low doses of ionizing radiation and its dose–effect relationship. Radiat Environ Biophys 2006b;44:245–251.

UNSCEAR 1988 Report. Ionizing radiation: sources and biological effects. New York, United Nations Publications.

UNSCEAR 2000 Sources and Effects of Ionizing Radiation. New York, United Nations Publications.

US NRC 2007: Staff comments on the draft recommendations of the ICRP. http://www.nrc.gov/reading-rm/doc-collections/commission/secys/2007/secy2007-0036/2007-0036scy.pdf

Verger P, Chérié-Challine L. Evaluation des conséquences sanitaires de l'accident de Tchernobyl en France. Rapport conjoint IPSN-InVS. Décembre 2000.

Verger P, Catelinois O, Tirmarche M, Chérié-Challine L, Pirard P, Colonna M, Hubert P.

Thyroid cancers in France and the Chernobyl accident: risk assessment and recommendations for improving epidemiological knowledge. Health Phys 2003;85:323-329.

Figure D.1.1 - Annual age-standardized incidence and mortality of thyroid cancer in France
(Remontet et al., 2003)

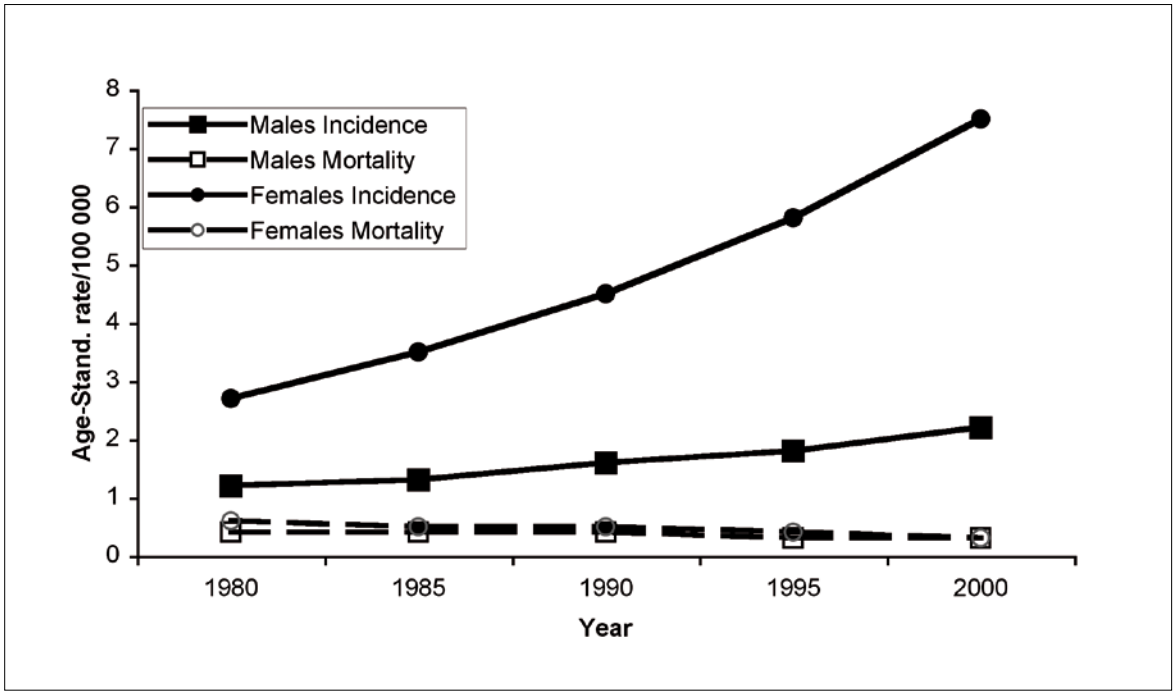
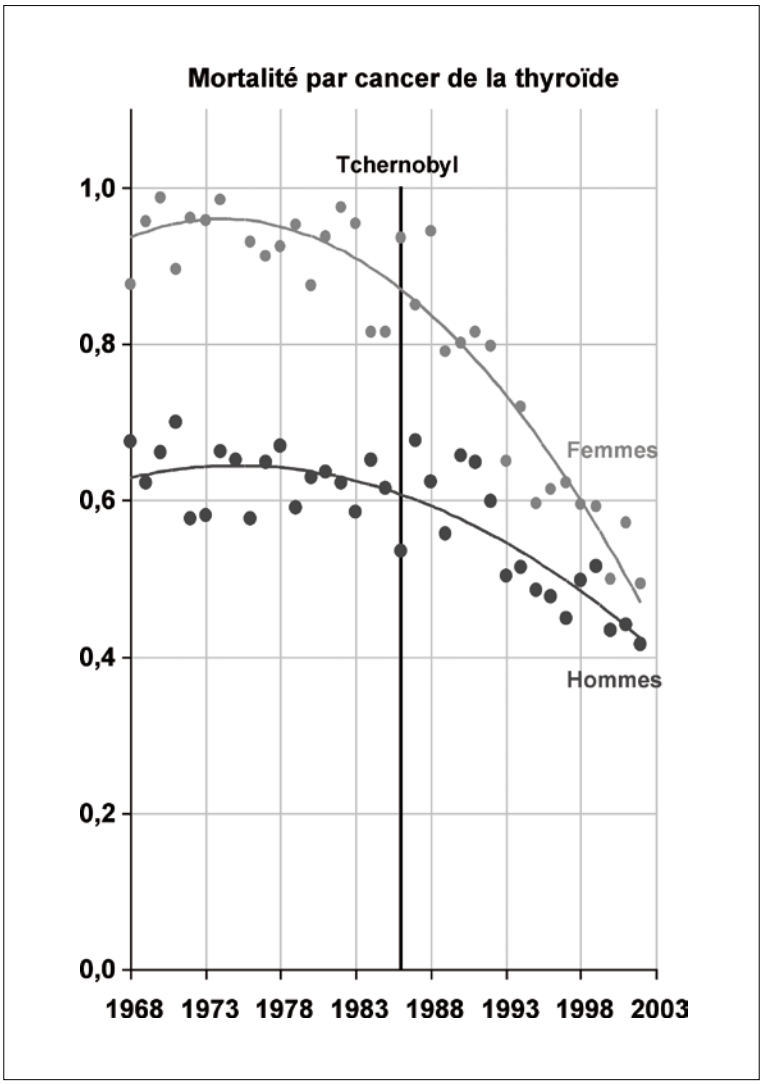


Figure D.1.2 - Mortality from thyroid cancer in France in deaths per 100 000, age-standardization on European Standard Population (Source: C. Hill, Institut Gustave Roussy)



Section D2: Established risk factors for cancer not included in the study

A causal association has been established between human cancer and various agents classified by IARC as Group 1 carcinogens to which a negligible proportion of the French population was or might have been exposed in 1985. Nonetheless, we briefly review these agents, without providing estimates for the number of cancers attributable to these factors.

1. Inorganic arsenic in drinking water

Inorganic arsenic in drinking water causes bladder, skin and lung cancers in humans (IARC, 2004). The most significant exposures, in terms of levels and populations, occur around the Gulf of Bengal, in South America and in Taiwan, China. In Europe, intermediate levels of arsenic in groundwater (below 200 µg/L) are found in areas of Hungary and Romania in the Danube basin, as well as in Germany, Greece and Spain. The studies showing an excess cancer risk have been conducted in areas with elevated arsenic content (typically above 200 µg/L), while the results of studies of bladder cancer conducted in areas with low or intermediate contamination are suggestive of a possible increased risk (IARC, 2004).

No data are available on the proportion of the population in France exposed to arsenic in drinking water, but it is known (Micquel, 2003) that in some regions including Alsace and the Massif central, arsenic levels may be high for up to 200.000 inhabitants which would result in few additional cancer cases each year.

There exist in France pockets of local soil and water contamination due to gold mines, e.g., in Salsigne (Aude). Gold miners from this area were exposed to high arsenic doses (and also to radon and silica) and had twofold higher mortality from lung cancer (Simonato et al., 1994). Excess deaths from lung, pharynx and digestive system cancers were reported in villages surrounding the industrial mining complex (Dondon et al., 2005).

2. Additional cancer risk factors

A number of additional chemical or physical agents, infections, lifestyles or geographical circumstances have been classified as Group 1 carcinogens by the IARC, that are not relevant to France. These factors include:

- Parasitic infections such as *Schistosoma haematobium*, involved in bladder cancer in Africa (IARC 1994c), and *Opisthorchis viverrini*, involved in liver cholangiocarcinoma in south-east Asia (IARC, 1994d). The prevalence of these infections is negligible in France.

- Aflatoxins are toxins produced by natural *Aspergillus* fungi *(A flavus, A nomius, A parasiticus)* that can be found in corn and raw peanuts (IARC, 2002). High intake of aflatoxins is associated with elevated rates of hepatocarcinoma. This association is found mainly in Africa and south-east Asia, where HBV carriers who eat food contaminated with aflatoxins have a more than 100-fold increase in liver cancer risk. Although contamination of foodstuffs may occasionally occur in France, its impact on liver cancer burden is likely to be minimal.

References

Dondon MG, de Vathaire F, Quenel P, Frery N. Cancer mortality during the 1968–94 period in a mining area in France. Eur J Cancer Prev 2005;14:297–301.

International Agency for Research on Cancer. Infection with schistosomes. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 61. Schistosomes, Liver Flukes and Helicobacter pylori. Lyon, IARC, 1994c, pp. 45–119.

International Agency for Research on Cancer. Infection with liver flukes. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 61. Schistosomes, Liver Flukes and Helicobacter pylori. Lyon, IARC, 1994d, pp. 121–175.

International Agency for Research on Cancer. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Vol. 82. Some Traditional Herbal Medicines, some Mycotoxins, Naphthalene and Styrene. Lyon, IARC, 2002.

International Agency for Research on Cancer. Arsenic in drinking-water. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Vol. 84. Some Drinking-water Disinfectants and Contaminants, including Arsenic. Lyon, IARC, 2004, pp. 39–267.

Micquel G. La qualité de l'eau et assainissement en France, Annexe 63 l'arsenic dans les eaux de boisson. Rapport OPECST N° 2152, 2002-2003

Simonato L, Moulin JJ, Javelaud B, et al. A retrospective mortality study of workers exposed to arsenic in a gold refinery in France. Am J Ind Med 1994;25:625–633.

Section D3: Factors suspected, but not demonstrated, to be causally associated with cancer in humans

A large number of risk factors have been linked to cancer risk in epidemiological studies. For most of them, the current evidence does not allow a conclusion as to the presence or absence of a causal relationship. The present review of avoidable causes of cancer in France is based on established risk factors, selected on the basis of evaluations made by authoritative international panels, chiefly within the IARC Monographs programme. It is not possible to review in detail all suspected causes of cancer. However, because of their importance in the public perception as important causes of cancer, in this chapter we discuss the evidence available for selected factors, including pollutants, non-ionizing radiation (other than UV light) and nutritional factors.

1. Diet

Epidemiological studies have found strong associations between diet and cardiovascular diseases, that have been largely reproduced in laboratory experiments. These findings have led to the development of efficient public health and pharmaceutical interventions. In contrast to cardiovascular diseases, diet and cancer remains at present a most difficult and complicated area of study. Doll and Peto (1981) estimated that 35% of cancer deaths in the USA could be attributable to dietary and nutritional practices, with, however, a wide "range of acceptable estimates" between 10% and 70%. These estimates have been widely quoted and used without comment by subsequent authors addressing the impact of nutrition on cancer burden. Most of the evidence available at the time of Doll and Peto's report was based on case–control studies, and selection and recall biases have been found to be particularly influential in nutrition-related investigations using the case–control design. More recently, Doll and Peto made new estimations according to which 25% of cancer deaths could be due to "diet", with a range of acceptable estimates of 15 to 35% (Doll and Peto, 2005). As for their 1981 estimates, Doll and Peto provided little detail on how these estimates were computed.

Many early studies consistently suggested a link between intake of dietary fat and increased risk of several common forms of cancer. However, several recent, well conducted large-scale cohort studies and randomized trials, conducted mainly in North America, have provided evidence against an major direct role of nutritional factors in cancer occurrence (e.g., for breast cancer: Michels et al., 2007; for colorectal cancer: Marques-Vidal et al., 2006). These studies also found evidence of a lack of association between fibre intake and risk of colorectal cancer (Michels et al., 2005; Park et al., 2005) and no evidence that fat intake influences the risk of colorectal cancer.

The evidence linking high intakes of fruit and vegetables to lower cancer risk has been reviewed by an IARC working group (IARC, 2003): there was no cancer for which the evidence was evaluated as sufficient to conclude that higher fruit or vegetable intake had a preventive effect.

Higher consumption of milk and calcium is associated with lower risk of colorectal cancer, with the inverse association for milk limited to cancers of the distal colon and rectum (Cho et al., 2004). Preserved meat and red meat probably increase the risk of colorectal cancer, but relative risks found so far are of the order of a 30% increase for very high versus very low intakes of red meat (Norat et al., 2005), which is quite lower than anticipated by results of ecological and case-control studies.

In contrast, the recent studies have underlined the role of obesity and overweight in many human cancers (e.g., colorectal cancer, breast cancer and pancreas cancer).

It is worth noting that an evidence-based attempt

to estimate the attributable burden of cancer in the Nordic countries did not try to provide an estimate for nutritional factors, because of lack of evidence of the implication of these factors in cancer occurrence (Olsen et al., 1997).

The importance of dietary factors in cancer must therefore be reconsidered. The following example suggests that one must be cautious with Doll and Peto's 2005 estimate that 25% of cancer mortality could be due to dietary factors. Suppose that a protective nutrient A confers a reduction in the mortality from oro-pharyngeal, oesophageal, gastric, pancreatic and colorectal cancer that reaches 20% among subjects in the highest (fifth) quintile of intake (Table D3.1), as compared to subjects with lowest intake (first quintile), with a linear relationship in the intermediate groups. The 20% reduction is a realistic figure, similar to results found in some of the best conducted studies.

Table D3.1 – Hypothetical population distribution and RR of a protective nutrient A in the French population

Categories	**1 (lowest intake)**	**2**	**3**	**4**	**5 (highest intake)**
% population in each category	20%	20%	20%	20%	20%
RR	1.00 (reference)	0.95	0.90	0.85	0.80

If all the population had an intake of nutrient A similar to that observed in the lowest quintile, i.e., everybody had minimal intake of nutrient A, there would be an 11% increase in cancer deaths associated with this nutrient A (Table D3.2), an increase that would correspond to 2.9% of all cancer deaths in males and 2.7% in females.

Table D3.2 – Theoretical numbers of cancer deaths attributable to protective nutrient A comparing a population whose distribution is presented in Table D3.1, and a population with 100% of subjects in the lowest quintile

	Males	**Females**
Oral cavity and pharynx	435	81
Oesophagus	386	77
Stomach	351	223
Colon-rectum	927	845
Pancreas	403	356
Total	**2502**	**1583**
% of all cancer	**2.9%**	**2.7%**

This example suggests that Doll and Peto's estimate of 25% of cancer mortality attributable to diet in their 2005 report was somewhat excessive. It is thus unlikely that the avoidance of still unknown dietary risk factors or the promotion of still unknown protective nutrients would lead to reductions in cancer mortality of the magnitude proposed by Doll and Peto. In Section E1, new working hypotheses on diet and cancer are presented.

2. Outdoor air pollution

Epidemiological studies and laboratory experiments in animals have shown that air pollution can influence all-cause mortality, mainly through its now well documented impact on acute cardiovascular events and on respiratory diseases. However, the effects of air pollution on cancer mortality, particularly lung cancer mortality, are still a matter of debate.

In most European countries, outdoor air quality has much improved in recent decades (WHO-Europe, 2003). A consistent finding of US and European studies on air pollution has been the steady decrease in air pollutant concentrations over time, and nowadays, on average, air in North American and European cities seems less loaded with particles than 10–20 years ago (e.g., Pope et al., 2002; Filleul et al., 2005).

Epidemiological studies on cancer risk from outdoor air pollution have been conducted for several decades and many definitions of outdoor air pollution exposure have been used. The IARC Monographs programme has not evaluated the carcinogenicity of outdoor air pollution as a complex mixture, although some of its components have been subject to separate evaluations, including benzo[a]pyrene (Group 1), several other polycyclic aromatic hydrocarbons (Groups 2A and 2B) and diesel engine exhaust (Group 2A) (see below). The lung is the main target organ of these agents.

Earlier studies generally compared residents of urban areas, where the air is considered more polluted, with residents of rural areas. For instance, in France, no difference has been found in cancer mortality according to the size of the city (Salem et al., 1999). However, this kind of so-called "ecological" study provides very limited data on typical levels of any pollutants in the areas studied and they are no longer considered as useful for assessing relationships between air pollution and diseases such as cancer.

Various indicators of air pollution used in relevant studies can be considered as three broad groups: (i) components of air pollution which are suspected to exert a carcinogenic effect *per se*, such as different fractions of fine particulate matter (especially particles having a median aerodynamic diameter smaller than 2.5 µm, or $PM_{2.5}$), (ii) components of air pollution which are not expected to cause cancer, but are considered markers of the main sources of pollution, such as sulfur oxides (markers of emissions from major industrial sources and residential heating) and nitrogen oxides (markers of traffic pollution), and (iii) indirect indicators such as residence near sources of pollution such as major industrial emission sources or heavy road traffic.

Boffetta and Nyberg (2003) published a detailed review of these studies, and the remainder of this section concentrates on epidemiological aspects of air pollution most relevant to this report.

Diesel engine exhaust

Diesel engine exhaust (DEE) was classified as a Group 2A carcinogen by the IARC, meaning that diesel engine exhaust was not a proven human carcinogen. However, IARC last evaluated diesel exhaust in 1989 (IARC, 1989). New studies are in progress in both the USA and Europe on health issues related to diesel engine exhaust. Three major cohort studies on diesel engine exhaust and lung cancer are almost complete and publication of their main results is expected soon. These are:

1. Extended follow-up of potash miners cohort in Germany. The first follow-up reported an RR for lung cancer of 2.2 (95% CI 0.8–6.0) (Saverin et al., 1999).
2. Cohort study of US miners.
3. Cohort study of US truckers.

Particulate matter

Particulate matter (PM) suspended in the air has received much attention during the past two decades, mainly since laboratory experiments have shown the ability of these particles to enhance tumorigenesis in animals.

In epidemiological studies, $PM_{2.5}$ particles are those most strongly associated with all-cause

mortality and cardiovascular mortality. Three cohort studies in the USA (Dockery et al., 1993; McDonnell et al., 2000; Pope et al., 2002; Laden et al., 2006) reported on the RR of lung cancer for exposure to $PM_{2.5}$, as measured in the areas of residence of the study subjects (Table D3.3). In all three studies, an increased risk of lung cancer was found for increased air concentrations of $PM_{2.5}$, although the increase was heterogeneous among studies and significant only in the largest of the three studies (Pope et al., 2002). None of the three studies found a significant association between other air pollutants (e.g., NO_2, SO_2, total suspended particles) and lung cancer mortality. The largest of the three studies (Pope et al., 2002) found that the association between exposure to $PM_{2.5}$ and lung cancer was essentially observed among never-smokers, and was restricted to individuals with education equal to or lower than high school, while a statistically significant inverse association was detected in individuals with more than high school education (Krewski et al., 2005). Similarly in the Adventist Health and Smog (AHSMOG) cohort study, the health effects of PM_{10} particles were restricted to non-smokers (Abbey et al., 1999).

The US studies on the long-term effects of air pollution on health and on cancer in particular can be criticized on the following points:

(i) It is unknown whether $PM_{2.5}$ represents a measure of air pollution relevant to its carcinogenic potential.

(ii) Relative risks of lung cancer associated with air pollution, in particular with $PM_{2.5}$ and PM_{10}, typically range between 0.9 and 1.3 (Table D3.3). In this range of values, relative risks are very sensitive to confounding. In studies such as CPS-II, the issue of residual confounding by smoking or other factors remains unresolved. For instance, smoking in a closed area produces about 10 times more $PM_{2.5}$ than a low-emission diesel engine (Invernizi et al., 2004). It follows that the highest air concentrations of $PM_{2.5}$ or PM_{10} particles are encountered in areas where people are smoking, mainly when smoking takes place indoors in non-ventilated rooms. The relative risks of lung cancer with $PM_{2.5}$ have been found to be significantly increased among non-smokers, and not at all among current smokers (Pope et al., 2002), and this effect might be due to residual confounding by indoor exposure to passive smoking. Furthermore, in the ACS study, fine particles were associated with increases lung cancer risk in subject with medium or low educational level but with significantly *decreased* lung cancer risk in subjects with higher education level (Krewski et al., 2005). This sizeable effect modification according to strata of a socio-economic indicator suggests residual confounding by other social class-related factors, such as occupational exposure to lung carcinogens.

(iii) The available data on exposure to air pollution, and to $PM_{2.5}$ in particular, are limited and refer to the present time or the recent past, and not to exposure that took place well before the studies were launched.

Studies on air pollution and lung cancer in Europe

The first European cohort study, in the Netherlands (Hoek et al., 2002) suggested that exposure to traffic-related air pollution including PM was associated with increased mortality from cardio-pulmonary diseases in subjects living close to main roads. Unfortunately, this study included too few subjects for proper assessment of the influence of air pollution on lung cancer (Table D3.3). Since then, other studies in Europe, such as the PAARC study in France and the GENAIR study in seven European countries (Table D3.3), have found no association between air pollutants and lung cancer.

Studies have been reported that suggest a possible increased risk of lung cancer from exposure to nitrogen oxides (NOx) (Hoek et al., 2002; Nafstad et al., 2003; Nyberg et al., 2000; Filleul et al., 2005). NOx is an indicator of exposure to outdoor air pollution, but interpretation of data on NOx exposure is not straightforward, as NOx may be a marker of exposure to a wide variety of components (Boffetta and Nyberg, 2003). Correlations between air concentrations of NOx and diesel engine exhaust (DEE) or particulate matter are stronger in Europe than in the USA. In this respect, the results of European studies on NOx strongly underline that further efforts must be made to determine what outdoor air pollution components or mixtures are relevant to lung carcinogenicity.

Table D3.3 – Relative risk (RR) of lung cancer and outdoor air pollution in studies with quantitative assessment of exposure to air particles; studies are ordered according to last year of follow-up

Location, study period, Reference	No. and sex	RR	95% CI	Exposure contrast	Basis for exposure assessment	Range, mean
ASHMOG study: Seventh-day Adventists USA, California, 1977–92 (McDonnell et al., 2000)	6338 M adults	2.23	0.56–8.94	per 24.3 µg/m3 $PM_{2.5}$	Residential history 1966–92 and local monthly pollutant estimates based on airport visibility data 1966–92	Mean (SD) PM2.5: 59.2 (16.8) µg/m3
The Netherlands, 1986–94 (Hoek et al., 2002)	4492 M+F, age 55–69 y	1.06	0.43–2.63	Exposure to 19.9 vs 10.6 µg/m3 of black smoke §	Traffic air pollutants (black smoke and nitrogen dioxide)	Mean (SD) (range) black smoke: 15.5 (3.2) (9.6–35.8) µg/m3
ASC/CPS-II USA, 1982–98 (Pope et al., 2002)	500 000 M+F adults	1.08	1.01–1.16	per 10 µg/m3 $PM_{2.5}$	City of residence in 1982. Pollutant averages of 1979–1983†	Mean (SD) PM2.5: 21.1 (4.6); study range roughly 5–30 µg/m3
Six US cities, extended follow-up USA, 1975–98 (Laden et al., 2006)	8111 M+F adults	1.27	0.96–1.69	per 10 µg/m3 $PM_{2.5}$	City of residence in 1975. Pollutant average 1979–85	Study range PM2.5: 34.1–89.9 µg/m3
PAARC survey, France, 1974–99 (Filleul et al., 2005)	14 284 M+F adults	0.97	0.93–1.01	per 10 µg/m3 black smoke §	Pollutants measured in 1974–76 and 1978–81 in 24 areas	Range black smoke: 18–152 µg/m3 in 1974–76
GENAIR study 7 European countries, 1990–1999 (7 years FU) (Vineis et al., 2006)	500 000 M+F adults*	0.91	0.70–1.18	per 10 µg/m3 PM_{10}	Place of residence. Traffic-related air pollution 1990–99	Study range PM10:19.9–73.4 µg/m3

* Nested case–control of lung cancer in 91 M + 180 F never-smokers matched with three controls for sex, age, smoking status, country of recruitment and time elapsed between recruitment and diagnosis.

† This study reported results for several other indicators of PM exposure, with results similar to those reported in the table

§ For results of other past studies on black smoke, see Boffetta and Nyberg (2003)

Since the publication of results from the USA, fine particles have received more attention in Europe, but there are still no representative data on average levels of exposure to fine particle pollution in Europe. A study based on 21 monitoring stations in European cities reported wide variations in fine particle concentrations, with mean values in winter in the range 4.8–69.2 µg/m3 $PM_{2.5}$ (median, 19.9 µg/m3) and in summer in the range 3.3–23.1 µg/m3 $PM_{2.5}$ (median, 14.8 µg/m3) (Hazenkamp-von Arx et al., 2003). Two French cities took part in this study: Grenoble (average level 12.9 µg/m3 $PM_{2.5}$ in summer and 28.0 µg/m3 $PM_{2.5}$ in winter) and Paris (15.9 µg/m3 $PM_{2.5}$ in summer and 21.0 µg/m3 $PM_{2.5}$in winter).

No studies in Europe have yet reported data on associations between $PM_{2.5}$ air concentrations and subsequent mortality from lung cancer, or other diseases. Therefore, studies in Europe gathering data on air pollutants have had recourse to relative risks from the American ASC/CPS-II study (Pope et al., 2002; Krewski et al., 2005) for estimating the fraction of lung cancer deaths attributable to $PM_{2.5}$. In France, a recent study in four cities (Paris, Grenoble, Rouen and Strasbourg) used the ASC/CPS-II relative risks and estimated that about 10% of lung cancers were attributable to $PM_{2.5}$ particles (Nerriere et al., 2005). There are three important reasons, however, why the use of these data to calculate an AF for air pollution in France requires caution:

(i) Air pollution in the USA and in Europe has different quantitative and qualitative characteristics; for instance, the higher proportion of diesel cars in Europe accounts for a greater concentration of black smoke. It is therefore not known whether RRs found in US cities are relevant to conditions prevailing in European cities (Katsouyanni, 2005).

(ii) In US cities, increases in RR for lung cancer with $PM_{2.5}$ were observed in never-smokers, while no increased RR was observed in current smokers. Hence, extrapolation of RRs found in US cities to any other place must take into account the proportions of current, former and non-smokers in the different study settings.

(iii) The increase in lung cancer mortality with increasing $PM_{2.5}$ concentration is not linear, being relatively steep below 15 µg/m3 but becoming slower above this concentration (Pope et al., 2002). Moreover, there is no information on RRs at $PM_{2.5}$ concentrations above 25 µg/m3. Thus application of the 8% increase in lung cancer mortality for each 10-µg/m3 elevation in $PM_{2.5}$ is probably not entirely valid, in particular for high $PM_{2.5}$ concentrations such as those prevailing in many European cities.

Air pollution and childhood cancer

A possible impact of air pollution on childhood cancer has been the subject of a recent review of epidemiological results from 15 studies in the USA, the Nordic countries, Italy, France, the United Kingdom and the Netherlands (Raaschou-Nielsen and Reynolds, 2006). The review found no association between various indicators of air pollution and childhood cancer. The review also underlined the poor quality of most studies on this subject.

The review by WHO-Europe on health effects of air pollution

In 2003, a report by the WHO Regional Office for Europe reviewed the health effects of air pollution, and concluded that “long-term exposure to current ambient PM concentrations may lead to a marked reduction in life expectancy. The reduction in life expectancy is primarily due to increased cardio-pulmonary and lung cancer mortality” (WHO-Europe, 2003). The conclusions on lung cancer were based on exactly the same epidemiological studies in the USA summarized in Table D3.3. However, this review did not properly address the issue of residual confounding by risk factors for lung cancer such as passive smoking, radon and occupational exposures, and did not examine why relative risks of lung cancer vary according to educational level. It also did not evaluate the reasons for differences in RR between smokers and non-smokers.

Conclusions on air pollution and cancer

There is thus a clear lack of consensus within the scientific community on the likely impact of air pollution on cancer, in particular lung cancer. Even scientists examining exactly the same data have

come to different conclusions.

It is biologically plausible that heavy levels of exposure to air pollution can cause lung cancer in humans, mainly when air pollution is heavy. However, apart from exceptional circumstances, levels of air pollution observed nowadays in most European and North American cities are usually lower than those observed in the past. The problems and limitations discussed above in assessing the carcinogenic impact of levels of air pollution prevailing 20 years ago in our countries precluded any estimation of the number of cancers attributable to this agent.

The best way to make further progress will be to organize new studies, taking into consideration the experience of prospective studies that were conducted in North America. In view of the uncertainties regarding air pollution and lung cancer, a consortium is being assembled in Europe, under the lead of the University of Utrecht (The Netherlands), to organize air quality assessments in different types of area throughout Europe in parallel with follow-up of disease occurrence and mortality in populations residing in these areas.

In conclusion, because of the uncertainties in the establishment of a causal association between outdoor air pollution and lung cancer risk and the fact that this agent has not been classified by IARC among the established human carcinogens (Group 1), we provided no formal estimate of the proportion of lung cancer attributable to it.

3. Residence near pollution sources

To pinpoint possible industrial emissions responsible for the suggested urban excess of lung cancer and leukaemia, populations living near point sources of air pollution have been studied.

Living near to filling stations or roads carrying heavy traffic could entail exposure to particulate matter (see above), diesel engine exhaust (see above) and benzene. One French study found an elevated risk of leukaemia in children living near filling stations, but no association with proximity of heavy road traffic (Steffen et al., 2004). In contrast, one Italian study found no increase in deaths from leukaemia in a cohort of filling-station attendants (Lagorio et al., 1994) and another found an increased leukaemia risk linked to residence near roads carrying heavy traffic, but none with proximity of filling stations (Crosignani et al., 2004).

Increased risks have been reported for living close to industries such as smelters, foundries, chemical industry and others with various emissions, with up to doubled risk, although confidence intervals were mostly wide (reviewed by Boffetta and Nyberg, 2003). Other studies have shown no relationship, however. In particular, a number of studies concerned residence near sources releasing inorganic arsenic into the air. Ecological studies suggested an increased lung cancer risk, while case–control studies provided mixed results (reviewed in Boffetta and Nyberg, 2003).

Mixed results have been obtained regarding waste dumping sites in relation to serious health conditions including cancer and congenital malformations[4] (Vrijheid 2002; Goldberg et al, 1999; Knox 2000; Jarup et al, 2002; Elliot et al, 2001). Some studies found moderate associations between living near solid-waste incinerators and non-Hodgkin lymphoma or congenital malformations (Floret et al., 2003; Cordier et al., 2004), but others did not (e.g., Morris et al., 2003) and a recent review concluded that so far, no consistent association had been found between living near a waste incinerator and cancer (Franchini et al., 2004).

Excess cancer risks found by ecological studies on residence near waste incinerators are typically in the range of 1 to 10%. In this range of values, residual confounding may play a major role in the apparent associations found (Elliot et al., 1996, 2000). It must be noted that modern waste landfills and incinerators reject less toxic substances into the air and soil than old facilities, and associations with cancer found in some epidemiological studies are related to old types of incineration facilities. In addition, many of the studies done on these topics to date are of sub-optimal quality, and further large-scale studies are needed, including use of biomarkers for exposure assessment.

4. Water chlorination by-products

Chlorination by-products result from the interaction of chlorine with organic chemicals, whose level determines

[4] Similarly to cancers, congenital malformations may also be caused by mutagenic agents. In an area where the presence of mutagenic agents is suspected, absence of increases in congenital malformation rates reinforces the likelihood that an absence of increased cancer incidence rates is not spurious.

the concentration of the by-products (IARC, 1991). Among the many halogenated compounds that may be formed, the most commonly found are trihalomethanes, including chloroform, bromodichloromethane, chlorodibromomethane and bromoform. Drinking, bathing and showering are the main sources of exposure. Concentrations of trihalomethanes depend mainly on water contamination by organic chemicals: average measurements from the USA are of the order of 10 µg/L for chloroform, bromodichloromethane and chlorodibromomethane, while those for bromoform are close to 5 µg/L (IARC, 1991). A pooled analysis of six epidemiological studies resulted in a summary RR of bladder cancer equal to 1.18 (95% CI 1.06–1.32) for exposure above 1 µg/L of trihalomethanes (Villanueva et al., 2004). One of the studies included in the pooled analysis was conducted in France (Cordier et al., 1993); among the controls included in this study, the prevalence of exposure above 1 µg/L was 16%. The interpretation of these data is complicated by several factors. The concentration of by-products in water varies depending on the presence of organic contaminants, which differs by geographical area and by season. In addition, people consume water outside their homes, which is seldom considered in epidemiological studies. Furthermore, although the possible confounding effect of smoking has been taken into account in several studies, confounding by other risk factors such as diet remains a possibility. Bearing in mind these limitations and assuming that a causal association does exist, the figures mentioned above would result in an attributable fraction of bladder cancer of 2.8%, corresponding to 252 incident cases and 91 deaths in men and 50 incident cases and 28 deaths in women. There is no consistent evidence of an effect on other cancers.

5. Pesticides

Several pesticides used in the past have been shown to cause cancer in experimental animals. Very few currently available pesticides are established experimental carcinogens, and none is an established human carcinogen. Studies in humans have failed to provide convincing evidence of an increased risk, even in heavily exposed groups (Siemiatycki et al., 2004).

Difficulties in interpreting the available evidence include the complex nature of exposure to pesticides, including variations in agents used over time and the relative rarity of cancers suspected to be due to pesticide exposure, such as lymphomas and sarcomas.

Childhood and in-utero exposure to pesticides have been the subject of a number of epidemiological studies that examined indoor and outdoor exposures (including use of insecticidal shampoos for treatment of pediculosis) and professional exposure of parents (e.g., Menegaux et al., 2006; Ma et al., 2002; Meinert et al., 2000; Flower et al., 2004; Reynolds et al., 2005; Fear et al., 1998; Kristensen et al., 1995; Daniels et al., 1997; Chen et al., 2005). Results were often contradictory, indicators were too crude for capturing complex exposures, and many studies had methodological limitations (Daniels et al., 1997). Also, a proportion of positive results (i.e., the finding of a statistically significant association) could be due to the large number of statistical tests performed on large data sets collected in these studies (Reynolds et al., 2005). Recall bias probably plays a major role in the apparent association between self-reported parental past exposures to pesticides and cancer occurring in the offpring (Shüz et al., 2003).

Some epidemiological studies that suggested an association between specific pesticides and cancer were often false positive results that were not confirmed by further studies with better study design and large samples. Section B.10 discusses the example of a false positive result for DDE (the active metabolic by-product of DDT) and breast cancer. The eventual effects of pesticides on human health remains however an open field for research.

A recent case-control study in the Department of Gironde (France) on a large sample of patients with brain tumours suggest that moderate to relatively high occupational exposure to pesticides would not be associated with brain tumours, but that heavy occupational exposure to pesticides would be associated with brain tumours (Provost et al., 2007). The few observational studies done on pesticides and brain cancer did not all find an association, and thus results from the Gironde study needs to be replicated.

Given the lack of evidence linking pesticide exposure to human cancer risk, no cases of cancer can be attributed to either occupational or non-occupational exposure to this group of agents.

6. Dioxins

2,4,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) is an experimental carcinogen with limited evidence of carcinogenicity in humans. It is classified as a Group 1 human carcinogen by IARC on the basis of strong evidence that the same mechanism (interaction with the Ah receptor) operates in experimental animals and in humans (IARC, 1997). However, no clear excess of cancer has been shown among heavily exposed populations, including chemical workers, US Veterans of the Vietnam war exposed to defoliants, and residents in contaminated areas. For instance, a study in the USA among four cohorts of workers in whom excess cancer rates were observed suggested that high TCDD exposure resulted in an excess of all cancers combined, without any marked site specificity (Steenland et al., 1999). The excess cancer was limited to the most highly exposed workers, with exposures that were likely to have been 100–1000 times higher than those experienced by the general population and similar to the TCDD levels used in animal studies.

The most serious disaster involving dioxins was the explosion at a chemical factory in Seveso, Italy, in July 1976 that resulted in the contamination of residents with high levels of TCDD. Follow-up of the whole population living in the contaminated areas, including linkage with the population-based cancer registry and with mortality registries, has been conducted and studies of this cohort have provided the most informative data on exposure to TCDD and cancer. The study defined three areas around the accident epicentre, one of very high and one of high exposure (zones A and B, around 5750 inhabitants in total) and one of lower exposure (zone R, around 30 000 inhabitants). Table D3.4 shows that in the long-term follow-up (20 years), no excess mortality or breast cancer incidence was detected in any of the three areas, although a small, non-significant excess of breast cancer mortality was reported in one of the intermediate follow-ups for women resident in zones A or B who were aged less than 55 years (Baccarelli et al., 1999; Bertazzi et al., 2001; Pesatori et al., 2003). The only cancers with significantly increased mortality were lymphomas and leukaemias, but only among residents in the area at lower contamination. Altogether, these results do not support a causal role of TCDD in cancer occurrence (Smith and Lopipero, 2001).

A further study was conducted on a subset of 981 women resident in zones A or B from whom serum samples were collected within five years of the accident and analysed for TCCD in 1996-98 (Warner et al., 2002). Fifteen women reported having been diagnosed with breast cancer, and the diagnosis was confirmed by pathology in 13 cases (in the follow-up study until 1991 for cancer incidence in the whole cohort, 23 cases of breast cancer were reported [Pesatori et al., 2001]). The serum TCDD level of cases was slightly higher than that of the whole group of women; after adjustment for risk factors of breast cancer, the RR for a $\log^{10}$ increase in TCDD level was 2.1 (95% CI 1.0-4.6). After exclusion of the two non-confirmed cases, this RR was no longer statistically significant, and the p-value of the test

Table D3.4 - 20-year mortality in dioxin-contaminated areas in Seveso, Italy (Bertazzi et al, 2001). Data are relative risks of dying from cancer among people residing in heavily (heavy) and less heavily (medium) contaminated areas around the disaster epicentre, compared with people residing in areas of low contamination

	No deaths	Heavy exposure	No deaths	Medium exposure
		(15-580 ppt)*		(1.7 - 4.3 ppt)
All causes	96	1.0 (0.9, 1.3)	649	1.0 (0.9, 1.1)
All cancers	27	0.9 (0.6, 1.3)	222	1.1 (0.9, 1.3)
Breast cancer	2	0.8 (0.2, 3.1)	12	0.7 (0.4, 1.3)
Leukemia, lymphoma	2	1.0 (0.8, 1.3)	26	1.9 (1.3, 2.7)

*Average acute exposure dose to dioxins in ppt (parts per trillion)

for trend in the categorical analysis was 0.07. Also, Warner's study was based on a subset of people who gave blood samples in the five years following the accident. Unlike Baccarelli et al., 1999, Bertazzi et al., 2001, and Pesatori et al., 2003, Warner et al. did not perform a proper follow-up of the cohort, but rather interviewed in 1996-98 (i.e., 20 years after the accident) the subset of women with blood samples who were still alive and living in the area (and willing to participate in their new study – about 80% of the original group). So, although in Warner's study, the results of the serum analysis of the subgroup of women living in zones A and B is suggestive of an association between TCDD exposure and breast cancer risk, a causal interpretation is not supported by the lack of increased incidence in the whole cohort, the self-reported nature of the definition of cases, the unclear temporal sequence of serum collection and cancer diagnosis (as some cancers might have been diagnosed around the time or after breast cancer diagnosis), the borderline statistical significance of the association and the lack of an association in other studies of TCDD-exposed women (IARC, 1997).

Given the uncertainties on the relationship between dioxin exposure and cancer risk, and the very small number of European residents likely to be exposed at doses comparable to those included in the available epidemiological studies, no estimate has been made of the number of cases of cancer in France attributable to dioxin exposure.

7. Use of indoor tanning equipment

Sunlight has been classified as a Group 1 carcinogen by the IARC (IARC, 1992). Similarly to UVB and UVA radiation, sunbeds have been classified by the IARC as an agent probably carcinogenic to humans (Group 2A) (IARC, 1992). Biological damage caused by exposure to sunbeds resembles that induced by sun exposure. Systematic review of epidemiological studies shows convincing evidence for increased risk of cutaneous melanoma (RR 1.7) due to sunbed use starting before 30 years of age (IARC, 2006; Gallagher et al., 2005; Veierød et al., 2003, 2004)[5].

In 1985, indoor tanning was very little used by the French population. Therefore, we have not made any estimate of impact of sunbed use on cutaneous melanoma occurrence in 2000. Incidence of cutaneous melanoma associated with indoor tanning will start increasing in 2010, as exposure rates in France increased greatly in the 1990s and 2000s. In 2001–02, about 13% of the French population below 50 years old were using sunbeds (Bataille et al., 2005).

8. Non-ionizing radiation other than UV light

Extremely low-frequency magnetic fields

People are exposed to electric and magnetic fields arising from a wide variety of sources. At extremely low frequencies (ELF), also called power frequencies (in the range 50 to 60 Hz), man-made fields are many thousands of times stronger than natural fields arising from the sun or the earth (IARC, 2002).

High-voltage power lines produce the highest electric field strengths that are encountered by people. The fields diminish with distance, however, and are considerably attenuated by objects; they are one to three orders of magnitude weaker inside homes than outside (NRPB, 2001). The major sources of electric fields inside buildings are therefore electrical appliances and current-carrying plumbing and/or electrical circuits. The electric field strength measured in the centre of a room is generally in the range 1–20 V/m, but close to appliances and cables, may increase to several hundred V/m (NRPB, 2001).

Magnetic fields, on the other hand, pass through most materials. The strength of magnetic fields produced by high-voltage power lines rapidly diminishes with distance and reaches background levels at distances of 50–300 metres from the power line, depending on the line design and current. For the general public, the highest magnetic flux densities are likely to be encountered in the vicinity of appliances or types of equipment that carry large currents. Typical exposure levels are of the order of 0.01–0.2 μT for magnetic fields, with 4–5% of the population having mean exposures above 0.3 μT and 1–2% having median exposures above 0.4 μT (Kheifets et al., 2006).

Health effects on humans related to this non-

[5] A comprehensive report by IARC including a systematic review with meta-analysis on artificial UV and skin cancer is available, and a summary of the report has been published in the International Journal of Cancer in 2006 (IARC, 2005, 2006).

ionizing type of radiation have been investigated in epidemiological studies for over two decades. The first report of an association between childhood cancer and power line exposure (Wertheimer and Leeper, 1979) has been followed by at least 24 studies on the same topic (Ahlbom et al., 2000; IARC, 2002).

Three recent meta-analyses have both shown a significant 1.7–2.0-fold excess of childhood leukaemia for mean and median exposures above 0.3 and 0.4 μT (Ahlbom et al., 2000; Greenland et al., 2000; Kheifets et al., 2006). The evidence linking exposure to ELF electric and magnetic fields with human cancer was evaluated by an IARC Monographs working group. ELF magnetic fields were classified as a possible human carcinogen (Group 2B), based on limited epidemiological evidence of an increased risk of childhood leukaemia for exposures above 0.4 μT (IARC, 2002). In the absence of conclusive evidence of a causal association between exposure to electromagnetic fields and cancer, no cases can be attributed to this agent. If a causal association were considered established, the attributable number of childhood leukaemias due to exposure to ELF fields would range between 100 and 2400 cases per year worldwide, representing between 0.2 and 5% of the 50 500 annual leukaemia cases worldwide in individuals below 15 years old (estimate from Globocan 2002, on www.iarc.fr).

There is inadequate evidence in humans for the carcinogenicity of ELF magnetic fields in relation to all other cancers (IARC, 2002). ELF electric fields were considered not to be classifiable as to their carcinogenicity to humans (Group 3) (IARC, 2002).

Cellular telephones

The frequency of signals emitted from cellular phones ranges between 450 and 2200 MHz, in the microwave/radiofrequency (RF) region of the electromagnetic spectrum. At present, the biological mechanism, if any, by which these signals might increase risk of cancer is unclear. While biological effects of RF fields at levels below current international guidelines have been confirmed (NRPB, 2001; AFSSE, 2005; Health Council of the Netherlands, 2007), there is at present little and inconsistent evidence of any carcinogenic effect in laboratory animals.

The relation between cancer risk and RF exposure from mobile phones has been the subject of a number of epidemiological cohort and case–control studies. Comprehensive reviews of the literature are conducted and updated periodically by a number of national radiation protection bodies (Boice and McLaughlin, 2002, for the Swedish Radiation Protection Authority; NRPB, 2001; AFSSE 2005; Health Council of the Netherlands, 2007). Most of the studies published to date, however, suffer from methodological limitations, including lack of information on the level of RF field exposure of individual study subjects, possible recall and selection bias (in case–control studies) and, importantly, limited numbers of subjects with long-term use of cellular phones.

Results are now appearing of analyses of national data-sets included in the INTERPHONE Study (Christensen et al., 2004, 2005; Hepworth et al., 2006; Lahkola et al., 2007; Lönn et al., 2004, 2005, 2006; Schoemaker et al., 2005; Schüz et al., 2006; Takebayashi et al., 2006), some of which suggest a possible increased risk of acoustic neurinoma and glioma in long-term users of cellular telephones. Upon their completion in 2007, the international analyses of the INTERPHONE study will add considerably to the body of scientific evidence on cellular phone use and cancer risk.

In conclusion, results available at present do not permit a definitive conclusion about a possible association between cellular telephone use and the risk of malignant and non-malignant tumours of the central nervous system or of the parotid gland.

9. Infectious agents

Human herpesvirus 8 (HHV8) was classified by the IARC as a Group 2A carcinogen (IARC Monograph No 70 1997). HHV8 is probably associated with Kaposi sarcoma and possibly other cancers, but formal evidence has been produced only recently.

References

Abbey DE, Burchette RJ, Knuttsen SF et al. Long-term inhalable particles and other air pollutants related to mortality in nonsmokers. Am J Resp Crit Care Med 1999;159:373-382.

AFSEE. Agence Française de Sécurité Sanitaire Environnementale. Téléphonie Mobile et

Santé., Paris, 2005.

Ahlbom A, Day N, Feychting M, et al. A pooled analysis of magnetic fields and childhood leukaemia. Br J Cancer 2000;83:692–698.

Baccarelli A, Pesatori A, Landi M, Consonni D, Bertazzi P. Long term endocrine related outcomes of 2,3,7,8-TCDD Exposure: The Seveso Mortality Study. Organohalogen Compounds 1999;42:43–47

Bataille V, Boniol M, DeVries E, et al. A multicentre epidemiological study on sunbed use and cutaneous melanoma in Europe. Eur J Cancer 2005;41:2141–2149.

Bertazzi PA, Consonni D, Bachetti S, et al Health effects of dioxin exposure: a 20-year mortality study. Am J Epidemiol 2001;153:1031–1044.

Boffetta P, Nyberg F. Contribution of environmental factors to cancer risk. Br Med Bull 2003;68:71–94.

Boice JD, McLaughlin JK. Epidemiologic Studies of Cellular Telephones and Cancer Risk – A Review. Swedish Radiation Protection Authority, SSI rapport : 2002:16. September 2002, ISSN 0282–4434

Chen Z, Stewart PA, Davies S, et al. Parental occupational exposure to pesticides and childhood germ-cell tumors. Am J Epidemiol 2005;162:858–867.

Cho E, Smith-Warner SA, Spiegelman D, et al. Dairy foods, calcium, and colorectal

cancer: a pooled analysis of 10 cohort studies. J Natl Cancer Inst. 2004;96:1015-1022.

Christensen HC, Schuz J, Kosteljanetz M, et al. Cellular telephone use and risk of

acoustic neuroma. Am J Epidemiol 2004;159:277–283.

Christensen HC, Schuz J, Kosteljanetz M, et al. Cellular telephones and risk for brain tumors: a population-based, incident case-control study. Neurology 2005;64:1189–1195.

Cordier S, Clavel J, Limasset JC, et al. Occupational risks of bladder cancer in France: a

multicentre case-control study. Int J Epidemiol 1993;22:403-411

Cordier S, Chevrier C, Robert-Gnansia E, et al. Risk of congenital anomalies in the vicinity of municipal solid waste incinerators. Occup Environ Med 2004;61:8–15.

Crosignani P, Tittarelli A, Borgini A, et al. Childhood leukemia and road traffic: A population-based case-control study. Int J Cancer 2004;108:596–599.

Daniels JL, Olshan AF, Savitz DA. Pesticides and childhood cancers. Environ Health Perspect 1997;105:1068–1077

Dockery DW, Pope CA 3rd, Xu X, et al. An association between air pollution and mortality in six U.S. cities. New Engl J Med 1993;329:1753–1759.

Doll R, Peto R. The causes of cancer: quantitative estimates of avoidable risks of cancer in the United States today. J Natl Cancer Inst 1981;66:1191–1308.

Doll R, Peto R. Epidemiology of cancer. In: Textbook of Medicine, 4th Edition, Oxford University Press, 2005, pp. 193–218.

Elliott P, Shaddick G, Kleinschmidt I, et al. Cancer incidence near municipal solid waste incinerators in Great Britain. Br J Cancer 1996;73:702–710.

Elliott P, Eaton N, Shaddick G, Carter R. Cancer incidence near municipal solid waste incinerators in Great Britain. Part 2: histopathological and case-note review of primary liver cancer cases. Br J Cancer 2000;82:1103–1106.

Elliott P, Briggs D, Morris S, et al. Risk of adverse birth outcomes in populations living near landfill sites. BMJ 2001;323:363–368.

Filleul L, Rondeau V, Vandentorren S, et al. Twenty-five year mortality and air pollution: results from the French PAARC survey. Occup Environ Med 2005;62:453–460.

Fear NT, Roman E, Reeves G, Pannett B. Childhood cancer and paternal employment in agriculture: the role of pesticides. Br J Cancer 1998;77:825–829.

Floret N, Mauny F, Challier B, et al. Dioxin emissions from a solid waste incinerator and risk of non-Hodgkin lymphoma. Epidemiology 2003;14:392–398.

Flower KB, Hoppin JA, Lynch CF, et al. Cancer risk and parental pesticide application in children of Agricultural Health Study participants. Environ Health Perspect 2004;112:631–635.

Franchini M, Rial F, Buiatti E, Bianchi F. Health effects of exposure to waste incinerator emissions: a review of epidemiological studies. Ann Ist Super Sanità 2004;40:101–115.

Gallagher RP, Spinelli JJ, Lee TK et al. Tanning beds, sunlamps, and risk of cutaneous malignant melanoma. Cancer Epidemiol. Biomarkers Prev 2005;14:562–566.

Goldberg MS, Siemiatyck J, DeWar R, et al. Risks of developing cancer relative to living near a municipal solid waste landfill site in Montreal, Quebec, Canada. Arch Environ Health 1999;54:291–296

Greenland S, Sheppard A, Kaune W, et al. A pooled analysis of magnetic fields, wire codes, and childhood leukemia. Epidemiology 2000;11:624–634

Hazenkamp-von Arx ME, et al. PM2.5 and NO2 assessment in 21 European study centres in ECRHS II; annual means and seasonal differences. Atmospheric Environ 2004;38:1943–1953.

Health Council of the Netherlands. Electromagnetic Fields: Annual Update 2006. The Hague, Health Council of

the Netherlands, 2007; publication no. 2007/06.

Hepworth SJ, Schoemaker MJ, Muir KR, et al. Mobile phone use and risk of glioma in adults: case-control study. BMJ 2006;332:883-887.

Hoek G, Brunekreef B, Goldbohm S, et al. Association between mortality and indicators of traffic-related air pollution in the Netherlands: a cohort study. Lancet 2002;360:1203–1209.

International Agency for Research on Cancer. Chlorinated drinking-water. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Vol. 52. Chlorinated Drinking water; Chlorination By-products; Some Other Halogenated Compounds; Cobalt and Cobalt Compounds. Lyon: IARC, 1991, pp. 45–141.

International Agency for Research on Cancer. Diesel and gasoline engine exhausts. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Vol. 46. Lyon, IARC, 1989.

International Agency for Research on Cancer. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Vol. 55, Solar and Ultraviolet Radiation. Lyon, IARC, 1992.

International Agency for Research on Cancer. Polychlorinated dibenzo-para-dioxins. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Vol. 69. Polychlorinated Dibenzo-para-dioxins and Polychlorinated Dibenzofurans. Lyon, IARC, 1997, pp. 33–343.

International Agency for Research on Cancer. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Vol. 70. Epstein-Barr Virus and Kaposi's Sarcoma Herpesvirus/Human Herpesvirus 8. Lyon IARC, 1997.

International Agency for Research on Cancer. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Vol. 80. Non-Ionizing Radiation, Part 1: Static and Extremely Low-Frequency (ELF) Electric and Magnetic Fields. Lyon, IARC, 2002.

International Agency for Research on Cancer. IARC Handbooks of Cancer Prevention Vol. 8, Fruit and Vegetables. Lyon, IARC, 2003.

International Agency for Research on Cancer. Exposure to Artificial UV Light and Skin Cancer. Report from an IARC Working Group, Lyon, 2006.

International Agency for Research on Cancer Working Group on artificial ultraviolet (UV) light and skin cancer. The association of use of sunbeds with cutaneous malignant melanoma and other skin cancers: A systematic review. Int J Cancer 2007;120:1116-1122

Invernizzi G, Ruprecht A, Mazza R, et al. Particulate matter from tobacco versus diesel car exhaust: an educational perspective. Tobacco Control 2004;13:219–221

Jarup L, Briggs D, de Hoogh C, et al. Cancer risks in populations living near landfill sites in Great Britain. Br J Cancer 2002;86:1732–1736.

Katsouyanni K. Long term effects of air pollution in Europe. Occup Environ Med 2005;62:432–433.

Kheifets L, Afifi AA, Shimkhada R. Public health impact of extremely low-frequency electromagnetic fields. Environ Health Perspect 2006;114:1532–1537.

Knox E. Childhood cancers, birthplaces, incinerators and landfill sites. Int J Epidemiol 2000;29:391–397.

Krewski D, Burnett R, Jerrett M, et al. Mortality and long-term exposure to ambient air pollution: ongoing analyses based on the American Cancer Society cohort. J Toxicol Environ Health 2005; Part A, 68:1093–1109.

Kristensen P, Andersen A, Irgens LM, et al. Cancer in offspring of parents engaged in agricultural activities in Norway: incidence and risk factors in the farm environment. Int J Cancer 1996;65:39–50.

Laden F, Schwartz J, Speizer FE, Dockery DW. Reduction in fine particle air pollution and mortality: Extended follow-up of the Harvard Six Cities study. Am J Respir Crit Care Med 2006;173:581–582.

Lagorio S, Forastiere F, Lavarone I, et al. Mortality of filling gas attendants. Scand J Work Environ Health 1994;20:331–338.

Lahkola A, Auvinen A, Raitanen J, et al. Mobile phone use and risk of glioma in 5 North European countries. Int J Cancer 2007;120:1769–1775

Lonn S, Ahlbom A, Hall P, Feychting M. Mobile phone use and the risk of acoustic neuroma. Epidemiology 2004;15:653–659.

Lonn S, Ahlbom A, Hall P, Feychting M. Long-term mobile phone use and brain tumor risk. Am J Epidemiol 2005;161:526–535.

Lonn S, Ahlbom A, Christensen HC, et al. Mobile phone use and risk of parotid gland tumor. Am J Epidemiol 2006;164:637–643.

Ma X, Buffler PA, Gunier RB, et al. Critical windows of exposure to household pesticides and risk of childhood leukemia. Environ Health Perspect 2002;110:955–960.

McDonnell WF, Nishino-Ishikawa N, Petersen FF, et al. Relationships of mortality with the fine and coarse fractions of long-term ambient PM10 concentrations in nonsmokers. J Expo Anal Environ Epidemiol 2000;10:427–436.

Marques-Vidal P, Ravasco P, Ermelinda Camilo M. Foodstuffs and colorectal cancer risk: A review. Clin Nutr 2006;25:14–36.

Meinert R, Schuz J, Kaletsch U, et al. Leukemia and non-Hodgkin's lymphoma in childhood and exposure to pesticides: results of a register-based case-control study in Germany. Am J Epidemiol 2000;151:639–646.

Menegaux F, Baruchel A, Bertrand Y, et al. Household exposure to pesticides and risk of childhood acute leukaemia. Occup Environ Med 2006;63:131–134.

Michels KB, Fuchs CS, Giovannucci E, et al.

Fiber intake and incidence of colorectal cancer among 76,947 women and 47,279 men. Cancer Epidemiol Biomarkers Prev 2005;14:842-849

Michels KB, Mohllajee AP, Roset-Bahmanyar E, et al. Diet and breast cancer: a review of the prospective observational studies. Cancer 2007; 109 (12 Suppl): 2712-2749.

Morris SE, Thomson AO, Jarup L, et al. No excess risk of adverse birth outcomes in populations living near special waste landfill sites in Scotland. Scott Med J 2003;48:105–107.

Nafstad P, Haheim LL, Oftedal B, et al. Lung cancer and air pollution: a 27 year follow up of 16 209 Norwegian men. Thorax 2003;58:1071–1076.

Nerriere E, Zmirou-Navier D, Desqueyroux P, et al. Lung cancer risk assessment in relation with personal exposure to airborne particles in four French metropolitan areas. J Occup Environ Med 2005;47:1211–1217.

Norat T, Bingham S, Ferrari P, et al. Meat, fish, and colorectal cancer risk: the European

Prospective Investigation into cancer and nutrition.J Natl Cancer Inst 2005;97:906-916.

NRPB. ELF Electromagnetic Fields and the Risk of Cancer. Report of an Advisory Group on Non-Ionising Radiation. Doc. NRPB, 12, No. 1, 1–179 (2001).

Nyberg F, Gustavsson P, Jarup L, et al. Urban air pollution and lung cancer in Stockholm. Epidemiology 2000;11:487–495.

Olsen JH, Andersen A, Dreyer L, et al. Avoidable cancers in the Nordic countries. APMIS 1997; 105 (Suppl 76):1–146.

Park Y, Hunter DJ, Spielgelman D, et al. Dietary fiber intake and risk of colorectal cancer: a pooled analysis of prospective cohort studies. JAMA 2005;14:2849–2857.

Pesatori AC, Consonni D, Bachetti S, et al. Short- and long-term morbidity and mortality in the population exposed to dioxin after the "Seveso accident".Industrial Health 2003, 41, 127–138.

Pope CA 3rd, Burnett RT, Thun MJ, et al. Lung cancer, cardiopulmonary mortality, and long-term exposure to fine particulate air pollution. JAMA 2002;287:1132–1141.

Provost D, Cantagrel A, Lebailly P et al. Brain tumours and exposure to pesticides: a case-control study in southwestern France. Occup Environ Med 2007; 64: 509-514

Raaschou-Nielsen O, Reynolds P. Air pollution and childhood cancer: A review of the epidemiological literature. Int J Cancer 2006;118:2920–2929.

Reynolds P, Von Behren J, Gunier RB, et al. Agricultural pesticide use and childhood cancer in California. Epidemiology 2005;16:93–100.

Salem G, Rican S, Jougla E. Atlas de la Santé en France–Les Causes de décès. Paris, Editions John Libbey, Eurotext, 1999.

Schuz J, Spector LG, Ross JA. Bias in studies of parental self-reported occupational exposure and childhood cancer. Am J Epidemiol 2003;158:710–716.

Schuz J, Bohler E, Schlehofer B, et al. Radiofrequency electromagnetic fields emitted from base stations of DECT cordless phones and the risk of glioma and meningioma (Interphone Study Group, Germany). Radiat Res 2006;166(1 Pt 1):116-119.

Shoemaker MJ, Swerdlow AJ, Ahlbom A, et al. Mobilephone use and risk of acoustic neuroma: results of the interphone case-control study in five North European countries. Br J Cancer 2005;93:842–848.

Siemiatycki J, Richardson L, Straif K, et al. Listing occupational carcinogens. Environ

Health Perspect 2004;112:1447-1459.

Smith AH, Lopipero P. Invited commentary: How do the Seveso findings affect conclusions concerning TCDD as a human carcinogen. Am J Epidemiol 2001;153:1045–1047.

Steenland K, Piacitelli L, Deddens J, et al. Cancer, heart disease, and diabetes in workers exposed to 2,3,7,8-tetrachlorodibenzo-p-dioxin. J Natl Cancer Inst 1999;91:779–786.

Steffen C, Auclerc MF, Auvrignon, et al. Acute childhood leukemia and environmental exposure to potential sources of benzene and other hydrocarbons: A case-control study. Occup Environ Med 2004;61:773–778.

Takebayashi T, Akiba S, Kikuchi Y, et al. Mobile phone use and acoustic neuroma risk in Japan. Occup Environ Med 2006;63:802–807.

Veierød MB, Weiderpasss E, Lund E, Thorn M, Hansson J, Armstrong BK, Adami HO. A prospective study of pigmentation, sun exposure, and risk of cutaneous malignant melanoma in women. J Natl Cancer Inst 2003, 95, 1530–1538.

Veierød MB, Weiderpasss E, Lund E, et al. Re: prospective study of pigmentation, sun exposure, and risk

of cutaneous malignant melanoma in women. J Natl Cancer Inst 2004;96:337–338.

Villanueva CM, Cantor KP, Cordier S, et al. Disinfection byproducts and bladder cancer: a pooled analysis. Epidemiol 2004;15:357–367.

Vineis P, Hoek G, Krzyzanowski M, et al. Air pollution and risk of lung cancer in a prospective study in Europe. Int J Cancer 2006;119:169–174.

Vrijheid M, Dolk H, Armstrong B, et al. and the EUROHAZCON collaborative group. Hazard potential ranking of hazardous waste landfill sites and risk of congenital anomalies. Occup Environ Med 2002;59:768–776

Warner M, Eskenazi B, Mocarelli P, et al. Serum dioxin concentrations and breast cancer risk in the Seveso Women's Health Study. Env Health Persp 2002; 110: 625-629.

Wertheimer N, Leeper E. Electric configurations and childhood cancer. Am J Epidemiol 1979;109:273–284.

WHO-Europe. Health Aspects of Air Pollution with Particulate Matter, Ozone and Nitrogen Dioxide. Report of a WHO Working Group, Bonn, Germany, 2003.

Discussion

Section E1: Knowledge gaps in causation of cancers : Progress made and further research needs

In their seminal work on the epidemiology of cancer, Doll and Peto (1981) estimated that about 80% of cancers have an identifiable cause related to lifestyle or environment. This estimate was derived essentially from the observation of considerable between-country differences in specific-cancer mortality and in lifestyle and environment.

In contrast to their evaluations, we conclude that in France in the year 2000, non-hereditary risk factors were identified for only around 50% of cancers in men and around 26% cancers in women (see Section C1). Other studies, based on approaches similar to the one adopted in this report, yielded results on attributable fractions of cancer for the Nordic countries and for the world (Olsen et al., 1997, Danaei et al., 2005) that were quite similar to those we found. Hence, a specific "cause" cannot be identified for a majority of cancers. This is not surprising in view of the insufficiency of our knowledge of carcinogenesis.

Since the 1950s, considerable means have been devoted to the identification of causes of cancer and the study of carcinogenesis, notably in the USA. The programme "Europe Against Cancer" of the European Commission from 1985 to 2000 succeeded in raising concerns about cancer causation and ways to control the disease in Europe. Huge progress in the understanding of carcinogenesis has been made, but these advances have raised new problems.

About 2–4% of cancers have an established genetic origin, being due to known mutations associated with higher cancer risk. However, genetic epidemiology and studies on twins (Lichtenstein et al., 2000) suggest that the hereditary component is greater. For instance, for breast and ovarian cancer, besides carriers of mutations in the BRCA1 and 2 genes, there is a notable proportion of familial cancers in which these genes are not mutated. In other types of cancer too, mutations of known genes are not sufficient to account for all hereditary factors (Kony et al., 1997). Considerable funds and energy have been devoted in the 1990s and 2000s to finding other variations in the genetic code and its expression in order to define the contribution of hereditary factors to the probability of cancer occurrence; but this is a long-term endeavour.

The aim of this section is to show that, despite the limitations of our current knowledge, recent advances in cancer biology are already sufficient to help in interpreting the epidemiological data. Carcinogenesis is such a large field of research that we shall not attempt to cover all of it. However, in order to put into perspective the epidemiological data, many of its facets merit discussion.

1. Carcinogenesis: a complex multi-step process

1-1 Complexity of carcinogenic processes

During the past two decades, new data have demonstrated that carcinogenesis is a far more complex process than previously suspected (Pitot and Dragan, 1994; Vogelstein and Kinzler, 1993, 2004; Ito et al., 1995; Trosko, 1997; Sjöblom et al., 2006; Sonnenschein and Soto, 2000; Tubiana, 2007) and research has focused on several new problems such as the role of reactive oxygen species (ROS) in DNA damage (Spitz et al., 2004), immunosurveillance,

and the defences against mutation and appearance of aberrant cells at the level of the cell, the tissue and the microenvironment. It is now recognized that cancer is not caused simply by the transformation of one cell, but also involves the reactions of the microenvironment and the tissue (Averbeck et al., 2006, Averbeck, 2007; Hanahan and Weinberg, 2000; Hahn and Weinberg, 2002; Park et al., 2003).

Berenblum and Shubik (1947) were the first to distinguish, through their experiments on the skin of rodents, two steps during carcinogenesis: *initiation*, which is caused by a genotoxic agent (the one they used was 7,12-dimethylbenz[a]anthracene (DMBA), and promotion, which was associated with the local application of croton ester oil or mechanical irritation. Mutations caused by genotoxic agents generally remain occult in the genome until a promoter agent is applied. In experimental animals, the time interval between initiation and promotion can be very long, which suggests that initiation is an irreversible step, probably linked to DNA damage in the stem cells. On the other hand, the interval between promotion and emergence of an invasive cancer is relatively constant. Observations in humans are consistent with experimental data. The interval between initiation and emergence of an invasive cancer can be very long. For example, following the atomic-bomb explosions over Hiroshima and Nagasaki, an excess of breast cancer was observed; but irrespective of the age at irradiation, the breast cancers in irradiated women were detected at the same age as in non-irradiated women. However, the excess of breast cancer is much greater when the age at irradiation is young (around age at menarche).

In the 1960s, *progression* was recognized as a third main step.

Armitage and Doll (1957) analysed the relationship between age and occurrence of cancer and concluded that cancer was due to accumulation in the genome of a single cell of 6 to 10 specific genomic damages. They thought that many of the events were occurring by chance and that carcinogenesis was a stochastic process. Later it was shown that the probability of such accumulation was extremely small in normal circumstances (Brash, 1997), but can be enhanced by several mechanisms (see Section 1-3-2).

1-2 The role of reactive oxygen species (ROS) in initiation

Aerobic living organisms have existed for at least 2.5 billion years. During oxygen metabolism, ROS are produced which are potent genotoxic agents (Burcham, 1999; Hsie et al., 1986; Guyton and Kensler, 1993; Klaunig et al., 1997; Feinendegen, 2002; De Bont and van Larebeke, 2004; Barnes and Lindahl, 2004). About 95% of molecular oxygen is converted into carbon dioxide and 5% into ROS (Barber and Harris, 1994). These ROS cause much DNA damage each day in each cell (Burkart et al., 1999, Cadet et al., 2004): about 55 000 single strand breaks, 8 double strand breaks (the most deleterious damage) and many other types of DNA damage.

The amount of DNA damage caused each day by ROS is similar to that induced by a radiation dose equal to 200 mSv per day (Burkart et al., 1999). During oxidative stress, which can be induced by several types of aggression, such as an infection or strenuous physical exercise (Dent et al., 2003; Bakkenist and Kastan, 2004), the number of ROS, and the resulting extent of DNA damage, can be much higher. DNA is a fragile macromolecule. Aerobic organisms would not have survived without effective repair mechanisms. Cell defences are activated during oxidative stress and they include: (i) the synthesis of anti-oxidant molecules (such as glutathione) and enzymatic systems which destroy ROS (such as catalase or superoxide dismutase, SOD), (ii) DNA repair, (iii) in multicellular organisms, since their appearance about 500 million years ago, control or elimination of mutant cells, which plays a crucial role in protecting the organism (Averbeck et al., 2006; Averbeck, 2007; Chandra et al., 2000).

1-3 Defence mechanisms

1-3-1 DNA repair. Most of the DNA repair systems present in mammalian cells existed already in yeast 800 million years ago, but have become more sophisticated during evolution. Almost nothing was known about DNA repair in 1980, but this has since become one of the main topics of cell biology research. It involves sensor molecules which constantly monitor DNA molecules. When a certain amount of damage is detected, signalling systems are triggered (e.g., the intranuclear ATM and ATR signalling systems), which

arrest cell progression and may activate DNA repair mechanisms, or apoptotic pathways (Averbeck et al., 2006; Averbeck, 2007, Bakkenist and Kastan, 2003; Christmann et al., 2003; Hoeijmakers, 2001; Jeggo and Lobrich, 2006; Sancar et al., 2004).

In a mammalian cell, several thousand genes are devoted to protecting the genome. Defects in the DNA repair systems are associated with much higher cancer incidence. For example, xeroderma pigmentosum is a disease in which DNA repair mechanisms following irradiation by solar ultraviolet rays are impaired. In these patients, the incidence of skin cancer is dramatically increased.

Most mutations are not caused by a genotoxic agent but are due to errors during DNA repair. These errors are very infrequent when the amount of cell damage is small, but their incidence increases markedly when the amount of DNA damage simultaneously present in a cell becomes greater, because the repair mechanisms then become more error-prone (Dikomey and Brammer, 2000); however, even when the amount of damage is limited, misrepair can occur.

Most genes that are associated with an increase in cancer incidence (for example, *BRCA1* and *BRCA2* in breast cancer) are genes that are involved in repair mechanisms and/or in cell progression throughout the cell cycle.

1-3-2 Elimination by death of cells with DNA damage

Elimination of cells with altered DNA plays a crucial role that was long overlooked (Guo and Hay, 1999; Sancar et al., 2004; Shiloh, 2003; Académie des Sciences – Académie de Médecine, 2005; Columbano et al., 1996; Chandra et al., 2000; Hickman, 2002).

When the amount of DNA damage in a cell is small, intranuclear signalling mechanisms may not be triggered and the cell dies (Rothkamm and Löbrich, 2003; Collis et al., 2004). Apoptosis, and other types of programmed cell death, eliminate cells with altered DNA or ones in which DNA damage has not been properly repaired, as well as aberrant cells of other types (Hickman, 2002; Schulte-Hermann et al., 1995).

A defect in apoptosis is a crucial step in carcinogenesis because it allows (i) the accumulation in the same cell of a large number of mutations and (ii) clonal amplification of the abnormal cells (Brash, 1997). The TP53 gene has a critical role in apoptosis and in the orientation of cells with DNA damage towards either DNA repair or apoptosis. It is mutated in over half of human cancers (Flores et al., 2002; Guo and Hay, 1999).

Apoptosis is not activated when the proportion of cells with DNA damage is too high, perhaps because it would dangerously enhance tissue injury (Académie des Sciences - Académie de Médecine, 2005).

1-3-3 Senescence, or loss of proliferation potential, is an alternative pathway for avoiding the transmission by a somatic cell of genetic defects to daughter cells. It is programmed and its importance has been recently underlined (Campisi, 2005; Schmitt, 2007).

1-4 Cancer initiation

As the first step towards carcinogenesis, initiation of cancer is linked to damage to the genome of a single cell (i.e., the monoclonal origin of human cancers) that succeeds in escaping the numerous control mechanisms preserving genomic integrity and tissue structure (Hanahan and Weinberg, 2000). It corresponds to a mutation conferring on a cell the ability to proliferate without a signal from a growth factor (for instance, when a proto-oncogene becomes an oncogene). All genotoxic agents, endogenous (such as ROS) or exogenous (such as solar ultraviolet radiation or ionizing radiation), can cause initiation.

Several broad types of mechanism can contribute to the accumulation of genomic damage possibly leading to cancer:

(i) *Genetic instability,* that is a greater propensity to accumulate DNA damage because of defects in DNA repair systems or because of a variety of mechanisms which induce chromosomal defects (e.g., aneuploidy) (Bjerkvig et al., 2005; Morgon, 2003; Li et al., 2001).

(ii) *Cell proliferation:* many human carcinogenic factors stimulate cell proliferation (for example, hormones, alcohol, energy-rich diet, and factors causing irritation, e.g., tobacco smoke). Greater cellular proliferation means higher numbers of mitoses that increase the likelihood of genomic defects (Ames and Gold, 1990; Cohen and Ellwein,

1990; Moore and Tsuda, 1998; Columbano et al., 1996).

(iii) *Amplification of subclones with apoptotic defects:* Normally, a cell that has incurred irrecoverable DNA damage (e.g., caused by a genotoxic or a mutagenic agent, but also by an error during mitotic processes) is self-eliminated by apoptosis. However, mutation (with inactivation) of critical genes implicated in cell-cycle regulation (e.g., the TP53 gene) and defects in apoptosis may allow the proliferation of cells that have accumulated DNA defects (Brash, 1997).

1-5 Promotion

The proliferation of initiated cells is generally prevented by the constraints exerted by the normal surrounding cells, the microenvironment and the tissue (Barcellos-Hoff, 2005; Tubiana 2007). There are many promoters that may overcome these constraints: endogenous (hormones such as estrogen for mammary cells, growth factors, etc.) or exogenous (alcohol, mechanical irritation, etc.). Inflammation and infections also have promoting effects (Takahashi et al., 2000). The proliferation rate reverts to normal when the promoter agent ceases to be present, unless a sub-clone has appeared that can proliferate without a promoter. The appearance of such a sub-clone marks the end of the promotion phase and opens the third phase of progression.

Promotion can also be caused by agents that alter intercellular communication such as phorbol esters. Foreign bodies such as asbestos can also perturb intercellular communication and may be carcinogenic through this mechanism (Klaunig, 1991; Rosenkranz et al., 2000; Yamasaki et al., 1995; Brand, 1982; Trosko et al., 2004).

1-6 Extracellular defences against carcinogenic processes

The development of an invasive cancer is opposed by defence mechanisms at the levels of microenvironment, tissue and body. At the tissue level, neighbouring cells control each other's proliferation (e.g., the role of cytokines) (Radisky and Bissell, 2004; Bhowmick et al., 2004; Barcellos-Hoff and Ravani, 2000; Barcellos-Hoff, 2005; Kalluri and Zeisberg, 2006; Liotta and Kohn, 2001). These mechanisms are probably similar to those active in embryogenesis and in tissue regeneration following an insult (Derksen et al., 2004; Giles et al., 2003; You et al., 2002; review in Beachy et al., 2004). Cancerous cells can not only overcome but also manipulate protective mechanisms, in order to be recognized as "friend" instead of being fought as "foe" (Mueller and Fusening, 2004). Many factors, such as infection and inflammation (Christen et al., 1999; Modugno et al., 2005), may contribute to enhancing cell proliferation of potentially malignant clones, facilitating the emergence of a clone of fully transformed cells.

Tissue disorganization, such as that caused by the death of a large number of cells or impairment of cell interactions, may facilitate the escape of potentially malignant cells from the tissue control system (Park et al., 2003). Tissue disorganization through disease also facilitates the escape of a sub-clone from the barriers of the microenvironment (Clark, 1995; Barcellos-Hoff and Ravani, 2000; Barcellos-Hoff, 2005). For example, liver cirrhosis facilitates the occurrence of a liver cancer; lung fibrosis (due to silicosis or asbestos) or chronic bronchitis (associated with tobacco) facilitate the occurrence of a lung cancer. Large amounts of any genotoxic agent, physical or chemical, kill a high proportion of normal cells and therefore induce proliferation by a compensatory homeostatic mechanism.

A promoting effect can also be caused by repeated exposure to a mutagenic agent; thus, chronic exposure to solar ultraviolet induces clonal amplification of sub-clones with an apoptosis defect (Brash, 1997).

1-7 Progression

During this last phase of carcinogenesis, preneoplastic cells become progressively more malignant, because during proliferation new mutations can occur and can originate new sub-clones (Cahill et al., 1999). Progression continues when the tumour has become an invasive cancer and increases its malignancy.

At the body level, immunosurveillance has the ability to control cancer progression, but when a cancer is clinically detectable, this is because the immune mechanisms have been overcome (Pardoll, 2001). Nevertheless, they can still be exploited in therapy (Taieb et al., 2006). Immunodepression

increases the incidence of several cancer types (Euvrard et al., 2003). Still at the body level, proteins can control or promote angiogenic phenomena and thus contribute to the inhibition or facilitation of the invasive properties of tumours arising in the organism (Folkman and Kalluri, 2004).

1-8 Genes involved in cancer

The sequencing of the human genome has paved the way for new avenues of research. Sequencing of DNA extracted from human tumours has revealed that the number of genes involved in carcinogenesis may be greater than previously assumed (Cancer Genome Atlas Project). The search continues for new genes or polymorphisms which may enhance the interaction between carcinogenic agents and the genome. Recently, it has been shown that about 300 micro-RNAs are present in the genome. They modulate the expression of several genes and their mutation or abnormal expression appears to affect carcinogenesis (Esquela-Kerscher and Slack, 2006; Thompson et al., 2006).

The existence of stem cells in tumours is now recognized (Monier, 2007) and it is highly probable that most human tumours derive from normal stem cells or progenitors. After DNA damage, stem cells may be more prone to apoptosis than to DNA repair (Cairns, 2002).

Some biological mechanisms implicated in cancer occurrence may not be directly related to DNA lesions, but to mechanisms mimicking DNA lesions or to events taking place in the cytoplasm and thus not requiring DNA lesions (Li et al., 2001). These mechanisms include epigenetic events such as DNA methylation and metabolic functions within and between cells, involving complex proteins and enzymatic functions.

Epigenetic phenomena are a growing field of cancer research (Baylin and Ohm, 2006; Gaudet et al., 2003; Konishi and Issa, 2007; Widschwendter et al., 2007; Schlesinger et al., 2007; Klochender-Yivin et al., 2002). They affect the expression of genes and the chromatin structure and play an important role in carcinogenesis. The occurrence of epigenetic phenomena involved in cancer is progressive and is not the result of stochastic processes.

Clearly, the previous concept which associated carcinogenesis with the mutation of a limited number of genes in one cell is no longer tenable (Trosko, 1997; Sjöblom et al., 2006). New concepts that have emerged during the past decade should have an impact on both the strategy of cancer prevention and the understanding of dose–carcinogenic effect relationships.

1-9 Interactions between endogenous and exogenous carcinogenic agents

Endogenous and exogenous carcinogenic agents are often intermingled during carcinogenesis, the exogenous being able to increase the probability of a cancer occurrence. However, a cancer can be caused by endogenous factors without the intervention of exogenous agents. Breast cancer, for example, is associated with exposure of mammary cells to sexual hormones and its incidence is much lower after an ovariectomy, which suppresses hormonal secretion (Rochefort, 2007). Conversely, the administration of estrogen for alleviating the symptoms associated with menopause increases breast cancer incidence by about 10% (Section B7). Thus one should not treat endogenous and exogenous factors as independent. In cancer prevention, both should be considered, but their respective roles vary with the type of cancer, lifestyle and environmental factors. 95% of lung cancers are due to tobacco and the same proportion of upper respiratory and upper digestive tracts cancers are due to the association of alcohol and tobacco. However, in the early 1960s in France among women, the proportion of lung cancer associated with tobacco was less than 30% because in 1945 most women did not smoke.

1-10 Examples of complexity of carcinogenic processes

Examples of the complexity of carcinogenic processes are numerous: for instance, in the lung, tobacco smoke is both a mutagenic factor and a source of chronic irritation and infection which enhances cell proliferation and tissue disorganization (Tubiana, 1999; Hazelton et al., 2005). The rapid decrease in lung cancer incidence after cessation of tobacco smoking underlines the prominent role of irritation and infection (even more rapid decreases in cardiovascular events are observed after smoking cessation, also linked to changes in inflammatory

phenomena in blood vessels).

Asbestos is a potent carcinogenic agent. Yet it is neither genotoxic nor mutagenic. The mechanism by which it causes genomic aberration is open to question and may simply involve tissue disorganization and interference with communication between cells (Brand, 1982).

In Africa, Burkitt lymphoma is due to the Epstein-Barr virus, but viral infection can lead to a clinical cancer only if an infant has been contaminated at a young age and if the body defences have been weakened by malaria (see Section B3). Burkitt lymphoma tends to disappear in African regions where malaria has become less common over time.

1-11 Summary

It now appears that while alteration of the genome of an initiated cell is a key event in carcinogenic processes, it is far from being sufficient to induce a cancer. Promotion could be more important. Currently, our insufficient understanding of the complexity of biological processes involved in carcinogenesis leads to difficulties in formulating hypotheses for the search for etiological factors. Cancer is caused not only by a mutation and the appearance of a neoplastic cell. It is also, and possibly mainly, a disease of the tissue, the microenvironment and intercellular communication.

2. Carcinogenic processes and cancer occurrence

The great complexity of carcinogenetic processes strongly suggests that a mutation in a cell has a very small likelihood of inducing an invasive cancer.

Among women with a mutated *BRCA1* or *BRCA2* gene, only about 50% will develop a breast cancer, although all mammary cells carry this defect (about 20 billion mammary cells, among which are about 200 million stem cells). These numbers show that the induction of such a mutation in a single cell has a very low (about 10-8) probability of inducing a breast cancer, even in a stem cell. This suggests that a small increase in the number of cells in which a mutation has been induced in a gene involved in the carcinogenic process can increase, but only modestly, the probability of cancer occurrence.

This conclusion is consistent with epidemiological data showing that promoters (hormones, alcohol) induce many more cancers than small doses of genotoxic agents. However, it should be recalled that high doses of genotoxic agents provoke cell proliferation and have a promoter action.

Another significant recent discovery is the long latent delay that can occur between an initiating event and the appearance of cancer induced by this event. For example, sixty years after the atomic bomb explosions in Japan, the incidence of colon cancer is still increased, slightly but significantly. Thus in the search for causes of cancer, more studies should be focused on risk factors during infancy, childhood and adolescence. Recent data revealing an association between the characteristics of a newborn and the probability of breast cancer fifty years later (Vatten et al., 2005) should encourage more investigation concerning gestation and infancy.

3. Dose–carcinogenic effect relationships and the effect of low doses

3-1 Assessing the carcinogenic effects of low doses

Assessment of risks associated with low-dose exposures has been one of the most controversial issues in oncology in recent years (Abelson, 1994; Ames and Gold, 1990, 1997). The inability of epidemiological surveys to detect evidence of a carcinogenic effect linked to low doses may be due to the insufficient statistical power of the studies, but also shows that the carcinogenic effect, if it exists (which is still debatable), is likely to be very small.

From a biological point of view, our current knowledge is compatible with the existence of a threshold (Académie des Sciences - Académie de Médecine, 2005; Feinendegen et al., 2007). Cells react efficiently to internal and external stresses. The various safeguard mechanisms protect the genome, to ensure the maintenance of genetic stability and to eliminate aberrant cells (see Section E1.1-3). The same types of complex systems of response and homeostatic regulation operate for aggression by endogenous (ROS) or exogenous (UV, ionizing radiation, chemical mutagens) agents. These systems encompass both repair of damage and prevention of further damage. But the main fact is that low doses of a genotoxic agent (for example, ionizing radiation) initiate biological responses that differ from those

observed at higher exposure. Low doses induce a delayed appearance of temporary changes in cellular signalling affecting intracellular enzyme activities, reactions to ROS, DNA repair, apoptosis, cell differentiation, and adaptive and immune responses (Feinendegen et al., 2007). These changes include a killing effect of preneoplastic cells (Portess et al., 2007), which may temporarily decrease the cancer incidence. The existence of a hormetic effect has long been debated but is now recognized, at least for experimental animals (Azzam et al., 1996; Calabrese, 2004). Adaptive responses show that when alerted by a challenge dose, cells can become more resistant to genotoxic agents (Wolff et al., 1988; Wolff, 1998; Rigaud and Moustacchi, 1996; Day et al., 2007, Tapio and Jacob, 2007).

Other phenomena, such as variations in mutations or carcinogenic effects with dose rate (Vilenchik and Knudson, 2000, 2006), modifications of phospho-proteome profiling in response to low or high doses of irradiation (Yang et al., 2006), low-dose hypersensitivity, and bystander effects (Mothersill and Seymour, 2006), confirm that responses to radiation (UV or ionizing) are modulated by dose. Indeed, activation of anti-oxidant defence, gene induction, DNA damage and signalling clearly differ at low or high exposure levels. Moreover, modern transcriptional analysis shows that the genes which are activated or repressed are not the same following a low or a high dose (Amundson et al., 2003; Franco et al., 2005). Moreover, the chronology of responses is different (Franco et al., 2005). Passive smoking is often quoted as an example of an agent that is carcinogenic at low doses. This conclusion is debatable. Passive smoking corresponds to 1 to 2 cigarettes smoked per day, that is, about 500 cigarettes per year, corresponding to a few grams of tar per year. This is far from being a low dose.

3-2 Extrapolations from carcinogenic effects of high-doses

Carcinogenic effects of low doses or concentrations of physical or chemical agents are generally estimated by an extrapolation based on a dose–effect relationship. The most widely used is the linear no-threshold (LNT) relationship, based on the assumption that (i) even the smallest dose of a carcinogen can cause a mutation which may initiate the carcinogenic process, (ii) the probability of initiation (per unit dose) is constant, irrespective of the dose, dose-rate or concentration, an assumption that is debatable because the efficacy of cell defence decreases with greater local time and spatial density of the damage (Dikomey and Brammer, 2000), and (iii) after the initiation of a cell, the carcinogenic process evolves similarly whatever the number of damaged cells in the microenvironment or the tissue. The discussion above (Section E1.1-3) shows that recent data are not consistent with these three assumptions.

Views opposing the LNT hypothesis have been expressed (Abelson, 1994; Ames and Gold, 1997; Feinendegen et al., 2007; Tubiana et al., 2006a,b; Yamamoto et al., 1998). Pasteur, 125 years ago, showed that inoculation of a small amount of micro-organisms can “vaccinate” against subsequent inoculations of large amounts of the same micro-organism. Adaptive responses that occur following an aggression by low doses of a genotoxic agent may correspond to a similar type of protective mechanism operating by a temporary up-regulation of defences (Feinendegen, 2007; Wolff et al., 1988; Wolff, 1998).

Currently, most regulations regarding carcinogens are based on the LNT relationship, despite its uncertain validity. In radioprotection (see Section D1), for example, the philosophy of the current recommendations is that there is no innocuous dose. Rather than defining a safe dose, this concept leads to the need to define what amount of risk is acceptable to society.

The joint report of the two academies (Académie des Sciences - Académie de Médecine, 2005) pointed out the drawbacks of the LNT hypothesis and its limitations. The absence of epidemiological data for low doses does not allow us to conclude that such doses have no carcinogenic effect but neither does it justify the use of LNT. For most carcinogens, the existence of a threshold is plausible due to the efficacy of defence mechanisms in the low dose range. In such cases, the use of LNT is not recommended because its drawbacks (the anxiety raised by risk overestimation and the cost of protective measures) can be greater than the advantages of the precautionary approach.

With regard to promotion or to epigenetic processes, LNT is even less scientifically plausible (Trosko, 1997). The existence of a threshold is highly probable when the carcinogenic agents are non-genotoxic promoting factors and for factors which

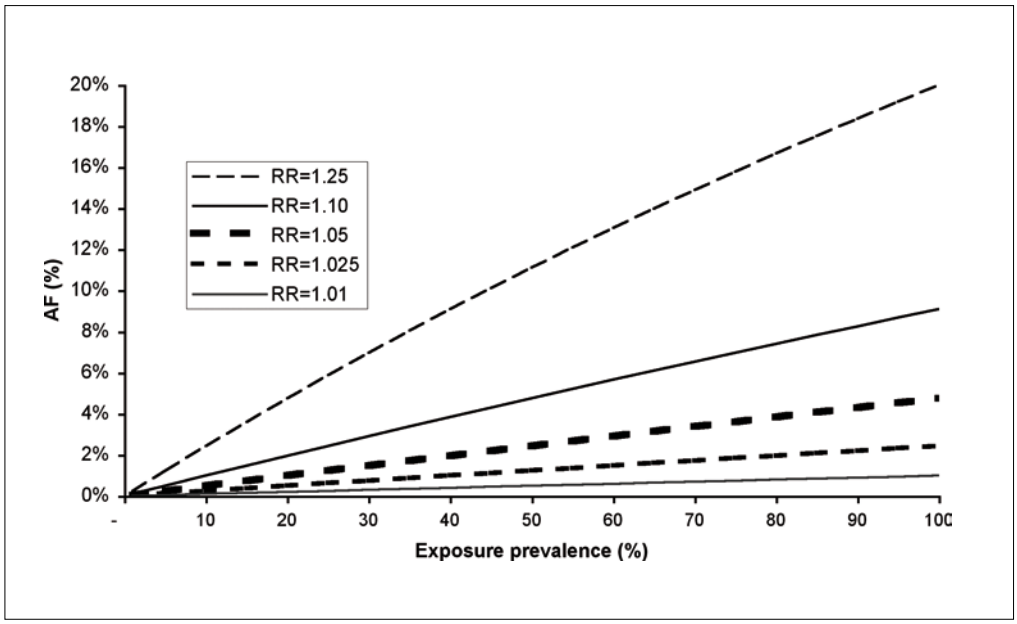
induce epigenetic transformation, but a threshold may also exist for genotoxic agents.

3-3 Statistical considerations on effects of low doses

A carcinogenic agent may be associated with a low relative risk of cancer (say, RR < 1.25) if exposure to that carcinogenic agent is limited to low doses. In the absence of a threshold and if a large proportion of the population is exposed to such low doses, a low risk factor could nevertheless have a low but observable impact on cancer incidence in the population. Figure E1.1 plots AFs according to exposure prevalence and for various levels of RR associated with exposure to low doses of a hypothetical carcinogenic agent. If the excess risk is less than 10% (i.e., RR = 1.10), then even if all the population were exposed to the agent, less than 10% of cancer would be due to that agent. It is only if the RR is higher that the proportion of cancer attributable to the agent increases substantially.

Because studying the effect of low doses poses formidable problems in epidemiology, most low-dose effects are derived from mathematical models that more or less assume that the type of risk factor–cancer relationship at low doses is similar to the relationships observed with medium and high doses. As previously discussed, this assumption is debatable for a number of reasons. Nevertheless, for some risk factors, low doses could theoretically be associated with specific effects on some biological events, including cancer, for instance, a chemical substance with hormone-like activity when acting at low dose on specific receptors, or hormones that have different types of biological activity at low and at higher concentrations (e.g., the so-called hormone-disruptors). The latter phenomenon, however, has never been observed in epidemiological studies and remains highly hypothetical.

Figure E1.1 - Attributable fraction of cancer to an agent in case of low RR



4. Not all cancers have an identifiable non-genetic cause

Exogenous genotoxic agents play a role in cancer by increasing the number of mutations, but, as previously discussed (Section E1.1-8), cancer initiation can occur without exogenous risk factors. Hence, for many cancers, it is probably illusory to expect to discover a specific causal factor explaining their occurrence.

Ageing is the main determinant of the incidence of several major cancers (e.g., colorectal cancer, prostate cancer). With ageing, a steadily greater proportion of cancer may not be due to specific exogenous causes, but rather to the probability that ageing cells accumulate biological "damage" or "errors", possibly leading to carcinogenic processes. Another possibility is less effective immunosurveillance.

5. Diet and nutritional factors

The most compelling evidence for a role for diet and nutritional factors in cancer occurrence comes from epidemiological studies of migrants and of declining stomach cancer incidence.

Migrant studies show that subjects moving from areas with a low incidence of several cancers, including colorectal and breast cancer, tend to acquire the cancer incidence levels of the host populations (e.g., Tomatis et al., 1990; McCredie et al., 1999, Maskarinec and Noh, 2004). This observation led to the hypothesis that nutrition was the predominant factor responsible. However, other factors than nutrition could also be involved (e.g., changes in reproductive factors in women, although this explanation cannot be evoked for colorectal cancer).

The dramatic decline in stomach cancer over the past 50 years in most industrialized countries is deemed to be partly due to changes in food preservation (e.g., refrigeration instead of salting or smoking) and nutritional habits (e.g., greater availability of fresh fruits and vegetables). A decline in *Helicobacter pylori* colonization of the stomach due to antibiotic treatment for other diseases or specific eradication of this bacterium has probably also contributed to the decrease in the stomach cancer burden (Tomatis et al., 1990).

Uncertainties about the role of nutritional factors arise from the apparent inability of epidemiological studies to identify critical nutrients or dietary patterns associated with cancer risk (Roe, 1979; Kolaja et al.,1996). Several new avenues being explored are outlined below, and new epidemiological and experimental studies are needed to examine the relevance of these concepts.

(i) Most prospective studies and interventional trials on nutrition and cancer have been performed in adults, whereas *in utero* life, childhood and adolescence probably represent periods of greater impact of nutritional factors that may be involved in cancer. Some data strongly suggest that diet during early age and during pregnancy may have an impact on cancer incidence during adulthood (Vatten et al., 2005). Nutrition (daily intake of calories) has a major impact on the secretion of several pituitary hormones, such as a growth factor which, in turn, strongly influences cell proliferation in specific tissues. Since 1950, the height of girls and boys in France and most other industrialized countries has dramatically increased (by over 10 cm in young adult age), as has their foot size; moreover the mean age at menarche has decreased by 2 to 3 years. In countries where diet is poor in protein or in calories, or where intestinal parasites are common, the height of children and adolescents is generally much smaller than in industrialized or affluent countries and varies with the socio-economic class; in these countries the incidence of breast and colon cancer is also much lower. When people migrate from these regions to developed countries (or when their lifestyle is "westernized", as in Singapore), their height increases, menarche occurs earlier and the incidence of breast and colon cancer rises. It has been hypothesized that these changes may be related to variations in hormonal balance. High levels of IGF1 and IGF2 are associated with higher incidence of breast and colorectal cancer (Hankinson et al., 1998; Khandwala et al., 2000; Schneid et al., 1992). Thus a high incidence of these types of cancer and higher height and early age at menarche might be related to higher levels of growth factors.

(ii) It is plausible that the effects of nutrition on cancer are exerted by unspecific factors such as the amount of calories, rather than by specific nutrients or foods (Elias et al., 2007; Kolaja et al., 1996; Roe, 1979). Animal experiments consistently show that total energy intake has more influence on

cancer occurrence than specific nutrients. In such experiments, notably in rodents, higher daily food intake is associated with shorter life expectancy and higher cancer incidence. The biological rationale behind the total energy hypothesis comes from the known link between mitotic activity and cancers of epithelial origin (e.g., colorectal cancer), and between high energy intake and mitotic activity (e.g., in the colon). In humans, overweight and obesity are also associated with increased cancer incidence, but we do not know whether or to what extent an increase in daily food intake has an impact on cancer incidence. The protective role of physical activity on colorectal and breast cancer is independent of weight (IARC, 2002) and could be related to biological mechanisms that are also influenced by energy intake. Daily food intake varies markedly from country to country; in France it has markedly increased during the past decade (even in individuals without overweight). The average daily food intake in France is now 3500 kcal/day/inhabitant. The average in developed countries is 3300 and in developing countries 2400, but it can be much lower in some countries, for example 1600 in Ethiopia. The impact of these variations of food intake on cancer incidence in humans has not yet been adequately studied.

(iii) Another new research avenue concerns the concept of "nutritional disequilibrium". Up to now, most studies have assessed cancer risk by comparing subjects having minimal, intermediate and maximal intake of nutrients. Nutritional disequilibrium is more concerned with the "best balance" between several nutrients, without reference to either too low or too high quantities of a given nutrient. The quality of the mix between nutrients could be the critical factor, instead of quantitative intake of specific nutrients.

6. Possible causes for underestimation of cancers associated with non-hereditary risk factors

6-1 Underestimation of the role of infectious agents

That infectious agents play a role in cancer occurrence has been known for over 40 years, and research on viruses and cancer has led to the unveiling of many basic biological mechanisms implicated in normal life and in carcinogenesis.

Many cancers are associated with viral, bacterial and parasitic agents. Some infectious agents are now known to be a necessary cause of a cancer, such as human papillomavirus (HPV) in cervical cancer. Occurrence of several other cancers is strongly related to infectious agents, e.g., *Helicobacter pylori* colonization for stomach cancer, chronic infection with hepatitis B and C viruses (HBV and HCV) for liver carcinoma, EBV for Hodgkin disease, and various viruses for some leukaemias.

Furthermore, cancers found with greater frequency in HIV-positive patients not treated with highly active antiretroviral agents (HAAR therapy) (e.g., Kaposi sarcoma and non-Hodgkin lymphoma (NHL)) show that some immune disorders associated with infections could be at the origin of several types of cancer. This hypothesis may also have a role in NHL and leukaemia occurring in HIV-negative subjects, who may have a genetic propensity to develop a cancer when infected with as yet unidentified infectious agents (Zur Hausen, 2006).

More and more epidemiological and laboratory data suggest that infectious agents may be direct or indirect causes of various cancers, including HPV in squamous carcinoma of the aerodigestive tract (Hammarstedt et al., 2006).

Infections could influence cancer occurrence through inflammatory processes that would have an impact on immune function and change the likelihood of developing cancer. Similar mechanisms could underlie the effect of agents acting on inflammatory processes to modify the likelihood of cancer, e.g., the anticancer effect of non-steroidal anti-inflammatory drugs, and the role of steroid hormones in endometrial cancer (Modugno et al., 2005).

Hence, it is expected that following further research, the proportion of cancer attributable to infectious agents will substantially increase.

6-2 Poor knowledge of the role of hormone-related factors

There is now consistent evidence that in women, hormones involved in reproductive function are implicated in breast and in gynaecological cancers (Rochefort, 2007). The reproductive function involves several hormones and much remains to be elucidated regarding their role in cancer; for instance, in breast

cancer, the respective roles of steroid hormones such as estrogenic, progesteronic and androgenic hormones, and of polypeptide hormones such as the growth hormone and prolactin remain to be clarified. While lifetime exposure to steroid hormones might promote breast cancer development, prolactin could represent a strong protective factor. Furthermore, peptide hormones and receptors involved in obesity and diabetes mellitus, but also in growth, could be far more efficient than steroid hormones for transformation of normal breast epithelial cells into cancerous cells of high malignant potential.

In spite of many gaps in knowledge, research on breast cancer has permitted a better understanding of the relationship between hormones and cancer and led to the discovery of efficient hormonal treatments (e.g., tamoxifen) (Rochefort, 2007). It is also hoped that breast cancer research will lead to the discovery of drugs for chemoprevention of the disease in healthy women.

6-3 Difficulty in assessing exposures accurately and the "risk dilution" or "misclassification" effect

Retrospective assessment of exposure in case–control epidemiological studies is often imperfect because most information provided by individuals is prone to bias (recall, interview, selection biases, etc.). Information from laboratory measurements in humans often focuses on one or few biological items that are not too difficult or expensive to measure. Use of past medical records is often limited by a lack of standardization of the data recorded.

Imperfections in exposure assessment generally lead to "misclassification" of an exposure–disease assessment[1], which results in finding increased (enhancing effect) or decreased (protective effect) risks of smaller magnitude (i.e., RR closer to unity (1.0)) than if perfect exposure measurement had been possible. Furthermore, most human cancers are not due to a single agent but to simultaneous or consecutive combinations of several agents (including complex mixtures) and epidemiological methods have poor ability to explore the effect of such mixtures.

There is clearly a need for some sort of "exposome" that could provide unbiased information on many exposures at the same time, incorporating the quality and quantity of exposures, and time relationships between exposures (Wild, 2005). Such an "exposome" would usefully supplement new laboratory analytical methods that screen DNA alterations (e.g., mutations) and variations (e.g., single nucleotide polymorphisms, SNPs), and phenomena occurring at epigenetic, proteinic and metabolic levels. For example, in the case of ionizing radiation, the study of aberrations in blood lymphocytes provides useful information regarding exposure (see Miller et al., 2001 for other examples). In that respect, there is a need to search for biomarkers that could (i) measure exposures, and (ii) identify individuals with biological characteristics making them more susceptible to cancer.

6-4 Difficulty in performing studies in children and adolescents

Most of what we know about the causes of cancer has been derived from studies in adults. However, research has gradually revealed that younger age and even *in utero* life is a period of higher susceptibility to carcinogens that has considerable repercussions on cancer occurrence during adulthood. This phenomenon was first recognized for ionizing radiation, and later for ultraviolet radiation and some medicinal products (e.g., diethylstilbestrol, DES). It is now suspected that the initial steps of some cancers may take place *in utero* or during the first years of life (e.g., testis cancer, cutaneous melanoma, some breast cancers). Infancy, childhood and adolescence seem pivotal for hormone-related cancers (e.g., breast, ovary, prostate) and probably also for cancers influenced by dietary habits (e.g., colorectal cancer and stomach cancer). A relationship has been observed between the size of the newborn and probability of breast cancer, suggesting the impact of *in utero* hormonal influence (Vatten et al., 2005).

Epidemiological research in minors poses considerable problems. The identification of suitable controls may be more problematic than with adults and in many countries the impossibility of collecting biological material (e.g., blood samples) from children or adolescents poses major limits on the scope of possible investigations. In addition, childhood exposure is difficult to assess both in retrospective

[1] Sometimes also called «dilution» of exposure-disease assesment.

studies (e.g., case–control studies) and in cancer-related prospective studies, because of the need for very long follow-up. Furthermore, numerous legal, moral and ethical barriers discourage the initiation of studies in children and when possible such studies are likely to be very expensive. Current developments in the legislative environment in North America and in Europe are further diminishing the prospects for conducting studies involving children. However, despite these difficulties and the very long timescale necessary for obtaining relevant information, cohort studies should be launched, because they would provide unique and important information.

7. Early detection and the emerging concept of "cancer without disease"

The availability of methods allowing detection of cancers at an earlier stage of development leads to substantial increases in cancer incidence. This increase is essentially due to the finding of cancers that cause no symptoms or clinical signs, that are more indolent and would probably never (or would take a long time to) become clinically apparent[2]. The issue of increased detection of tumours having histological characteristics of cancer, but not the clinical features of cancer, was already raised by Doll and Peto (Appendix C of their 1981 publication) and other authors (Fox, 1979).

In the past, many of these indolent tumours remained unidentified and never caused death. Thus their detection can be considered as an undesirable side-effect of screening. The treatment applied is often similar to that of potentially more dangerous cancers because, at present, it remains hard to predict the short-term or long-term outcome of small cancers on the basis of available clinical, histological, imaging and laboratory parameters. In this respect, the increase in cancer incidence and in overtreatment induced by early-detection methods may also be viewed as a consequence of the fact that diagnosis of cancer is based on histological criteria, rather than on criteria allowing prediction of the likely clinical course of the disease. Many of the small tumours would not evolve into invasive disease, i.e., they are "cancers without disease" (Folkman and Kalluri, 2004).

It remains to be determined whether indolent screen-detected cancers are associated with risk factors found to be associated with symptomatic or clinically apparent cancers. For several organs, the answer is likely to be negative. For instance, spontaneous formation of small tumours having cancerous histological characteristics takes place in the thyroid of many subjects (mainly in females), but most will never evolve into life-threatening disease. The spectacular increase in thyroid cancer incidence observed in many countries in the last decades parallels the advent of new exploratory tools, such as ultrasonography with high-frequency probes and fine needle biopsy methods, and does not seem to be related to changes in exposure to yet unknown risk factors. The clinical studies carried out for early detection and treatment of neuroblastoma in children have not resulted in lower mortality, which strongly suggests that most of these small screen-detected tumours would not have led to an invasive cancer (Schilling et al., 2002; Woods et al., 2002).

Another example is prostate cancer. Up to now, no consistent environmental or lifestyle risk factor has been definitely identified for this cancer and prostate cancer occurrence is largely associated with ageing. The incidence of prostate cancer has dramatically risen in populations where testing for prostate-specific antigen (PSA) has become widespread (See Section A2). Many of the prostate cancers found by PSA testing would have remained clinically silent, and probably most of these should not be associated with an environmental or lifestyle risk factor.

It is therefore possible to hypothesize that the net impact of early-detection methods increases the proportion of cancers for which there is no real environmental or lifestyle risk factor, so that the proportion of cancers for which such risk factors may account is decreased. In this respect, AFs estimated in this report are probably more valid for mortality data than for incidence data.

[2] In addition to indolent cancers, finding of in situ cancers is also considerably increased by early detection methods. These are tumours that have not developed beyond the basal membranes separating the epithelium from the conjunctival stroma. Before widespread availability of mammographic screening, in situ breast cancers represented less than 2% of all breast tumours, while they may now represent up to 20%. In situ cancers have low malignant potential, but in many organs, the likelihood of transformation into invasive cancer is uncertain, and therefore, treatment is often similar to that of invasive cancer. Note that regardless of malignant potential to evolve into an invasive cancer, some in situ tumours (e.g., in the breast) may be voluminous and require extensive surgery. Normally, cancer incidence data only include invasive cancers, and in situ cancers should not be counted as incident cancers. However, on needle biopsies, it can be difficult to distinguish in situ and invasive cancer in a small specimen of a small tumour.

References

Abelson PH. Risk assessment of low level exposure. Science 1994;265:1507.

Académie des Sciences – Académie de Médecine. Rapport conjoint n° 2 (mars 2005). Relation dose-effet et estimation des risques cancérogènes des faibles doses. Edit Nucleon –Paris (www.academiemedecine.fr/actualites/rapports.asp).

Ames BN, Gold LS. Too many rodent carcinogens: mitogenesis increases mutagenesis. Science 1990;249:970-971.

Ames BN, Gold LS. Environmental pollution, pesticides and the prevention of cancer:misconceptions. FASEB J 1997;11:1041-1052.

Amundson SA, Lee RA, Koch-Paiz CA et al. Differential responses of stress genes to low dose-rate gamma irradiation. Mol Cancer Res 2003;1:445-452.

Armitage P, Doll R. A two stage theory of carcinogenesis in relation to the age distribution of human cancer. Br.J. Cancer 1957;9:161-169.

Averbeck D. Mécanismes de défense à l'échelon cellulaire. Comptes Rendus Acad Sc 2007.

Averbeck D, Testard L, Boucher D. Changing views on ionizing radiation-induced cellular effects. Int J Low Radiation 2006;3:117-134.

Azzam EI, de Toledo SM, Raaphorst GP, et al. Low-dose ionizing radiation decreases the frequency of neoplastic transformation to a level below the spontaneous rate in C3H 10T1/2 cells. Radiat Res 1996;146:369-373

Baffis V, Shrier I, Sherker AH, et al. Use of interferon for prevention of hepatocellular carcinoma in cirrhotic patients with hepatitis B or C infection. Ann Inter Med 1999;131:696-701

Bakkenist CJ, Kastan MB. DNA damage activates ATM through intermolecular autophosphorylation and dimer dissociation. Nature 2003;421:499-506.

Bakkenist CJ, Kastan MB. Initiating cellular stress responses. Cell 2004;118:9-17.

Barber DA, Harris SR. Oxygen free radicals and antioxidants:A review. Am Pharmacy 1994;NS34:26-35.

Barcellos-HoffM.H., Integrativeradiationcarcinogenesis: interactions between cell and tissue responses to DNA damage. Sem Cancer Biol 2005;15:138-148.

Barcellos-Hoff MH, Ravani SA. Irradiated gland mammary stroma promotes tumorogenic potential by unirradiated epithelial cells. Cancer Res 2000;60:1254-1260.

Barnes DE, Lindahl T. Repair and genetic consequences of endogenous DNA base damage in mammalian cells. Annu Rev Genet 2004;38:445-476.

Baylin SB, Ohm JE. Epigenetic gene silencing in cancer – a mechanism for early oncogenic pathway addiction. Nature Reviews/Cancer 2006;6:107-116.

Beachy PA, Karhadkar, Berman D. Tissue repair and stem cell renewal in carcinogenesis. Nature 2004;432:324-331.

Berenblum I, Shubik P. The role of croton oil applications, associated with a single painting of a carcinogen, in tumour induction of the mouse skin. Br J Cancer 1947;1:379-382.

Bhowmick NA, Chytil A, Plieth D, et al. TGF-beta signaling in fibroblasts modulates the oncogenic potential of adjacent epithelia. Science 2004;303:775-777.

Bjerkvig R, Tynes BB, Aboody KS, et al. Opinion:the origin of the cancer stem cell: current controversies and new insights. Nature Reviews/Cancer 2005;5:899-904.

Brand KG. Cancer associated with asbestosis, schistomatosis, foreign body or scar. In: Becker, ed. Cancer: A Comprehensive Treatise. New York, Plenum Press, 1982; pp.661-692.

Brash DE. Sunlight and the onset of skin cancer. Trends Genet 1997;13:410-414.

Burcham PC. Internal hazards: baseline DNA damage by endogenous products of normal metabolism. Mutat Res 1999;443:11-36.

Burkart W, Jung T, Frasch G. Damage pattern as a function of radiation quality and other factors. Comptes-rendus Acad. Sc. III 1999;322:89-101.

Cadet J, Bellon S, Douki T et al. Radiation-induced DNA damage: formation, measurement, and biochemical features. J Environ Pathol Toxicol Oncol 2004;23:33-43.

Cahill DP, Kinzler KW, Vogelstein B, et al. Genetic instability and Darwinian selection in tumors. Trend Genet 1999;15:M57-M61.

Cairns J. Somatic stem cells and the kinetics of mutagenesis and carcinogenesis. Proc Natl Acad Sci USA 2002;99:10567-10570.

Calabrese EJ. Hormesis: from marginalization to mainstream: a case for hormesis as the default dose-response model in risk assessment. Toxicol Appl Pharmacol 2004;197:125-136.

Campisi J. Senescent cells, tumor suppression and organism aging. Cell 2005;120:513-522.

Chandra J, Samali A, Orrenius S. Triggering and modulation of apoptosis by oxidative stress. Free Radic Biol Med 2000;29:323-333.

Christen S, Hagen TM, Sigenaga MK, et al. Chronic inflammation, mutation and cancer. In: Microbes and

Malignancy: Infection as a Cause of Cancer. Parsonnet J and Horning S, eds. Oxford, Oxford University Press,1999, pp. 35-88.

Christmann M, Tomici MT, Roos WP, et al. Mechanisms of human repair: an update. Toxicology 2003;193:3-34.

Clark WH. The nature of cancer: morphogenesis and progressive self-disorganization in neoplastic development and progression. Acta Oncologica 1995;34:3-21.

Cohen SM, Ellwein LB. Cell proliferation in carcinogenesis. Science 1990;249:503-504.

Collis SJ, Schwaninger JM, Ntambi AJ, et al. Evasion of early cellular response mechanisms following low level radiation-induced DNA damage. J Biol Chem 2004;279:49624-49632.

Columbano A, Endoh T, Denda A et al. Effects of cell proliferation and cell death (apoptosis and necrosis) on the early stages of rat hepatocarcinogenesis. Carcinogenesis 1996;17:395-400.

Danaei G, Vander Hoorn S, Lopez AD, et al. Comparative Risk Assessment collaborating group (Cancers). Causes of cancer in the world: comparative risk assessment of nine behavioural and environmental risk factors. Lancet. 2005;366:1784-1793.

Day TK, Zeng G, Hooker AM et al. Adaptive response for chromosomal inversions on pKZ1 mouse prostate induced by low doses of X radiation delivered after a high dose. Radiat Res 2007;167:682-692.

De Bont R, van Larebeke N. Endogenous DNA damage in humans: a review of quantitative data. Mutagenesis 2004;19:169-185.

Dent P, Yacoub A, Contessa J, et al. Stress and radiation-induced activation of multiple intracellular signalling pathways. Radiat Res 2003;159:283-300.

Derksen PW, Tjin E, Meijer HP, et al. Illegitimate Wnt signaling promotes proliferation of multiple myeloma cells. Proc Natl Acad Sci USA 2004;101:6122-6127.

Dikomey E, Brammer I. Relationship between cellular radiosensitivity and non-repaired double-strand breaks studied for different growth states, dose rates and plating conditions in a normal human fibroblast line. Int J Radiat Biol 2000;76:773-781.

Doll R, Peto R. The causes of cancer: quantitative estimates of avoidable risks of cancer in the United States today. J Natl Cancer Inst. 1981;66:1191-1308.

Elias SG, Peeters PH, Grobbee DE et al. Transient caloric restriction and cancer risk. Cancer Causes Control 2007;18:1-5.

Esquela-Kerscher A, Slack FJ. Oncomirs microRNAs with a role in cancer. Nature Reviews/Cancer 2006;6:259-269.

Euvrard S, Kanitakis J, Claudy A. Skin cancer after organs transplantation. New Eng. J. Med. 2003;348:1681-1691.

Feinendegen LE. Reactive oxygen species in cell responses to toxic agents. Human & Experimental Toxicology 2002;21:85-90.

Feinendegen LE, Pollycove M, Neumann RD. Whole body responses to low-level radiation exposure. New concepts in mammalian radiobiology. Experim Hematol 2007;35:37-46.

Flores ER, Tsai KY, Crowley D et al. P63 and p73 are required for p53-dependant apoptosis in response to DNA damage. Nature 2002;416:560-564.

Folkman J, Kalluri J. Cancer without disease. Nature 2004;427:787-787.

Fox M. On the diagnosis and treatment of breast cancer. JAMA 1979;241:489-494.

Franco N, Lamartine J, Frouin V et al. Low-Dose exposure to _ rays induces specific gene regulations in normal human keratinocytes. Radiation research 2005;163:623-635.

Gaudet F, Hodgson JG, Eden A, et al. Induction of tumors in mice by genomic hypomethylation. Science 2003;300:489-492.

Giles RH, Van Es JH, Clevers H. Caught up in a Wnt storm: Wnt signaling in cancer. Biochim Biophys Acta 2003;1653:1-24.

Guo N, Hay BA. Cell proliferation and apoptosis. Cur Opin Cell Biol 1999;11:745-752.

Guyton KZ, Kensler TW. Oxidative mechanisms in carcinogenesis. Br Med Bull 1993;49:523-544.

Hahn WC, Weinberg RA. Rules for making human tumor cells. New Engl J Med 2002;347:1593-1603.

Hammarstedt L, Linquist D, Dahlstrand H, et al. Human papilloma virus as a risk factor for the increase in incidence of tonsillar cancer. Int J Cancer 2006;119:2620-2623.

Hanahan D, Weinberg RA. The hallmarks of cancer. Cell 2000;100:57-70.

Hankinson SE, Willette WC, Colditz GA, et al. Circulating concentrations of insulin-like growth factor-I and risk of breast cancer. Lancet 1998 ;351:1393-1396.

Hazelton WD, Clements MS, Moolgavkar SH. Multistage carcinogenesis and lung cancer mortality in three cohorts. Cancer Epidemiol Biomarkers Prev 2005;14:1171-1181.

Hickman JA. Apoptosis and tumorigenesis. Cur Opin Cell Biol 2002;12:67-72.

Hoeijmakers JHJ. Genome maintenance mechanisms for preventing cancer. Nature 2001;411:366-374.

Hsie AW, Recio L, Katz DS, et al. Evidence for reactive

oxygen species inducing mutation in mammalian cells. Proc Natl Acad Sci USA 1986;83:9616-9620.

International Agency for Research on Cancer. IARC Handbooks of Cancer Prevention Vol 6, Weight Control and Physical Activity. Lyon, International Agency for Research on Cancer, 2002.

Ito N, Hagawa R, Imoida K et al. Concepts in multistage carcinogenesis. Crit Rev Oncol Hematol 1995;21:105-33.

Janne PA, Mayer RJ. Chemoprevention of colorectal cancer. New Eng J Med 2000;342:1960-1968.

Jeggo P, Lobrich M. Radiation-induced DNA damage responses. Radiat Prot Dosimetry 2006;122:124-127.

Kalluri R, Zeisberg M. Fibroblasts in cancer. Nature Reviews/Cancer 2006;6:392-401.

Khandwala HM, McCutcheon IE, Flyvbierg A, et al. The effects on insulin-like growth factors on tumorigenesis and neoplastic growth. Endocr Rev 2000;21:215-244.

Klaunig JE. Alterations in intercellular communication during the stage of promotion. Proc Soc Exper Biol Med 1991;198:688-692.

Klaunig JE, Xu Y, Bachowski S, et al. Free-radical oxygen-induced changes in chemical carcinogenesis. In: Wallace KB, ed. Free Radical Toxicology. London, Taylor and Francis, 1997 pp. 375-400.

Klochender-Yivin C, Muchard et Yaniv M. SWI/SNF chromatin remodelling and cancer. Curr Op Genet Develop 2002;12:73-79.

Kolaja KL, Bunting KA, Klaunig JE. Inhibition of tumor promotion and hepatocellular growth by dietary restriction in mice. Carcinogenesis 1996;17:1657-1664.

Konishi K, Issa JP. Targeting aberrant chromatin structure in colorectal carcinoma. Cancer J 2007;13:49-55.

Kony SJ, de Vathaire F, Chompat A, et al. Radiation and genetic factors in the risk of second malignant neoplasms after a first cancer in childhood. Lancet 1997;350:91-96.

Li CY, Little J, Zhang W, et al. Persistent instability in cancer cells induced by non-DNA-damaging stress exposure. Cancer Res 2001;61:428-432.

Lichtenstein P, Holm LV, Verkasalo PK, et al. Environmental and heritable factors in the causation of cancer. Analyses of cohorts of twins from Sweden, Denmark and Finland. New Engl J Med 2000;343:78-85.

Liotta LA, Kohn EA. The microenvironment of the tumor-host interface. Nature 2001;411:375-379.

Maskarinec G, Noh JJ. The effect of migration on cancer incidence among Japanese in Hawaii. Ethnicity and Disease 2004;14:431-439.

McCredie M, Williams S, Coates M. Cancer mortality in migrants from the British isles and continental Europe to New South Wales, Australia, 1975-1995. Int J Cancer 1999;83:179-185.

Modugno F, Ness RB, Chen C, et al. Inflammation and endometrial cancer: an hypothesis. Cancer Epidemiol Biomarkers Prev 2005;14:2840-2847.

Miller AB, Bartsch H, Boffetta P, Dragsted L, Vainio H, eds Biomarkers in Cancer Prevention (IARC Scientific Publications No 154), Lyon, IARC, 2001.

Monier R. Avancées récentes sur la cancérogenèse. Comptes-rendus de l'Académie de Médecine (in press).

Monier R, Tubiana M. Avancées récentes sur la cancérogenèse. Comptes-rendus de l'Académie de Médecine (in press). 2007

Moore MA, Tsuda H. Chronically elevated proliferation as a risk factor for neoplasia. Eur J Cancer Prev 1998;7:353-385.

Morgon WF, Non-targeted and delayed effects of exposure to ionizing radiation. II. Radiation-induced genomic instability and bystander effects in vivo, clastogenic factors and transgenerational effects. Radiat Res 2003;159:581-596.

Mothersill C, Seymour CB. Radiation-induced bystander effects and the DNA paradigm: an "out of field" perspective. Mutat Res 2006;59:5-10.

Mueller MM, Fusening NE. Friends or foes – Bipolar effects of the tumour stroma in cancer. Nature Reviews/ Cancer 2004;4:639-649.

Olsen JH, Andersen A, Dreyer L, et al. Avoidable cancers in the Nordic countries. APMIS 1997;105:Suppl 76.

Pardoll DT Cells and tumors. Nature 2001;411:1010-1012.

Park CCD, Henshall-Powell RL, Erikson AC et al. Ionizing radiation induce heritable disruption of epithelial cell interactions. Proc Nat Acad Sc USA 2003;100:10728-10733.

Pitot HC, Dragan YP. The multistage nature of chemically induced hepato-carcinogenesis in the rat. Drug Metab Rev 1994;26:209-220.

Portess DI, Bauer G, Hill MA, et al. Low-dose irradiation on nontransformed cells stimulates the selective removal of precancerous cells via intercellular induction of apoptosis. Cancer Res 2007;67:1246-1253.

Radisky DC, Bissell MJ Cancer. Respect thy neighbor! Science 2004;303:774-775.

Rigaud O, Moustacchi E. Radioadaptation for gene mutation and the possible molecular mechanisms of the adaptive response. Mutat Res 1996;358:127-134.

Rochefort H. Cancérogenèse hormonale chez la femme: des mécanismes à la prévention. Comptes Rendus

Acad Sciences, Paris, 2007.

Roe EJ. Food and cancer. J Human Nutrition 1979;33:405-415.

Rosenkranz HS, Pollack N, Cunningham AR. Exploring the relationship between the inhibition of gap junctional intercellular communication and other biological phenomena. Carcinogenesis 2000;21:1007-1011.

Rothkamm K, Löbrich M. Evidence for a lack of DNA double-strand break repair in human cells exposed to very low x-ray doses. Proc Natl Acad Sci USA 2003;100:5057-5062.

Sancar A, Lindsey-Boltz LA, Unsal-Kaçmaz K, et al. Molecular mechanisms of mammalian DNA repair and the DNA damage checkpoints. Ann Rev Biochem 2004;73:39-85.

Schilling FH, Spix C, Berthold F et al. Neuroblastoma screening at one year of age. New Engl J Med 2002;346:1047-1053.

Schlesinger Y, Straussman R, Keshet I, et al. Polycomb-mediated methylation on Lys27 of histone H3 pre-marks genes for de novo methylation in cancer. Nat Genet 2007;39:232-236.

Schmitt CA. Cellular senescence and cancer treatment. Biochim Biophys Acta 2007;1775:5-20.

Schneid H, Seurin D, Noguiez P, et al. Abnormalities of insulin-like growth factor (IGF-I and IGF-II) genes in human tumor tissue. Growth Regul 1992;2:45-54.

Schulte-Hermann R, Bursch W, Grasl-Kraupp B, et al. Apoptosis and multistage carcinogenesis in rat liver. Mutat Res 1995;333:81-87.

Shiloh Y. ATM and related protein kinases: safeguarding genome integrity. Nature Reviews Cancer 2003;3:155-168.

Sjöblom T, Jones S, Wood LD et al. The consensus coding sequences of human breast and colorectal cancers. Science 2006;314;268-274.

Sonnenschein C, Soto A. Somatic mutation theory of carcinogenesis. Why it should be dropped and replaced? Mol Carcinogen 2000;29:1-7.

Spitz DR, Azzam EI, Li JJ, et al. Metabolic oxidation/reduction reactions and cellular responses to ionizing radiation: a unifying concept in stress response biology. Cancer Metastasis Rev 2004;23:311-322.

Taieb J, Chaput N, Menard C, et al. A novel dendritic cell involved in tumor immunosurveillance. Nature Medicine 2006;12:214-219.

Takahashi S, Ikeda Y, Okochi E, et al. Mutation induction by mechanical irritation caused by uracil induced urolithiasis in Big Blue rats. Mutat Res 2000;447:275-280

Tapio S, Jacob V. Radioadaptive response revisited. Radiat Environ Biophys 2007;46:1-12.

Thomson JM, Neuman M, Parkes JS, et al. Extensive post transcriptional regulation of micro RNAs and its implication for cancer. Genes Dev 2006;20:2202-2207.

Tomatis L, Aitio A, Day NE, Heseltine E, Kaldor J, Miller AB, Parkin DM, Riboli E, eds. International Agency for Research on Cancer. Cancer:Causes, Occurrence and Control. IARC Scientific Publications No 100, Lyon, IARC, 1990.

Trosko JE. Challenge to the simple paradigm that 'carcinogens' are 'mutagens' and to the in vitro and in vivo assays used to test the paradigm. Mutat Res 1997;373:245-249.

Trosko JE, Chang CC, Upham BL, et al. Ignored hallmarks of carcinogenesis: stem cells and cell-cell communication. Ann NY Acad Sci 2004;1028:192-201.

Tubiana M. Contribution of human data to the analysis of human carcinogenesis. Comptes Rendus Acad Sc, Sciences de la vie / Life sciences 1999;322:215-224.

Tubiana M. Progrès des connaissances sur la cancérogenèse. Comptes Rendus Acad Sc 2007.

Tubiana M, Aurengo A, Averbeck D, Masse R. The debate on the use of linear no threshold for assessing the effects of low doses. J Radiol Prot 2006a;26:317–324.

Tubiana M, Aurengo A, Averbeck D, Masse R. Recent reports on the effect of low doses of ionizing radiation and its dose–effect relationship. Radiat Environ Biophys 2006b;44:245–251.

Vatten LJ, Lund Nilsen TI, Tretli S et al. Size at birth and risk of breast cancer: prospective population based studies. Int J Cancer 2005;114:461-464.

Vilenchik MM, Knudson AG. Inverse radiation dose-rate effects on somatic and germ-line mutations and DNA damage rates. Proc Natl Acad Sci USA 2000;9:5381-5386.

Vilenchik MM, Knudson AG. Radiation dose-rate effects, endogenous DNA damage, and signalling resonance. Proc Natl Acad Sci USA 2006;103:17874-17879.

Vogelstein B, Kinzler K.W. The multistep nature of cancer. Trends Genet 1993;9:138-141.

Vogelstein B, Kinzler K.W. Cancer genes and the pathways they control. Nature Medicine 2004;10:789-799.

Widschwendter M, Fiegl H, Egle D, et al. Epigenetic stem cell signature in cancer. Nat Genet 2007;39:157-158.

Wild CP. Complementing the genome with an ''exposome'': The outstanding challenge of environmental exposure measurement in molecular epidemiology. Cancer Epidemiol Biomarkers Prev 2005;14:1847-1850.

Wolff S. The adaptive response in radiobiology: evolving insights and implications. Environ Health Perspect

1998;106:277-283.

Wolff S, Afzal V, Wienke JK, et al. Human lymphocytes exposed to low doses of ionizing radiations become refractory to high doses of radiation as well as to chemical mutagens that induce double-strand breaks in DNA. Int J Radiat Biol 1988;53:39-49.

Woods WG, Gao RN, Shuster JJ, et al. Screening of infants and mortality due to neuroblastoma. New Engl J Med 2002;346:1041-1053.

Yamamoto O, Seyama T, Ito A, et al. Oral administration of tritiated water (THO) in mouse. III: Low dose-rate irradiation and threshold dose-rate for radiation risk. Int J Radiat Biol 1998;73:535-541.

Yamasaki H, Mesnil M, Omori Y, et al. Intercellular communications and carcinogenesis. Mutat Res. 1995;333:181-188.

Yang F, Stenoien DL, Strittmatter EF et al. Phosphoproteome profiling of human skin fibroblast cells in response to low- and high-dose irradiation. J Proteome Res 2006;5:1252-1260.

You Z, Saims D, Chen S, et al. Wnt signaling promotes oncogenic transformation the inhibiting c-Myc-induced apoptosis. J Cell Biol 2002;157:429-440.

Zur Hausen H. Infections Causing Human Cancer. Weinheim, Wiley-VCH, 2006.

Section E2: General discussion

This study shows that in France, in the year 2000, tobacco smoking and alcohol drinking were by far the main risk factors of cancer; tobacco accounting for 27% of the total cancer burden in men and 6% in women, and alcohol accounting for 11% of the total burden in men and 4% in women. Infectious agents, obesity and overweight, physical inactivity, ultraviolet radiation, occupation and hormone treatment each accounted for 1 to 3.3% of the total cancer burden in men or in women. Reproductive factors and air, soil, food and water pollutants each accounted for between 0.1% and 1% of the total cancer burden. For pollutants, we considered only IARC Group 1 carcinogens. If suspected carcinogens such as outdoor air pollution with fine particles had been considered, pollutants could account for around 1% of all cancers.

This study was based on established carcinogenic agents (i.e., IARC Group 1 carcinogens), i.e., agents for which there is sufficient evidence for carcinogenicity in humans. Most relative risks were derived from the most recent meta-analyses of observational epidemiological studies. A few attributable fractions (AFs) were not derived from relative risks and data on exposure, but from AFs directly estimated for entire populations (i.e., those for sun exposure, EBV infections, and occupational asbestosis). A model approach was never used. We never had recourse to estimations based on expert opinion.

The AF estimates presented in this report are to be considered as minimal estimates, as we are aware that prevalence of some exposures may be underestimated (e.g., infections). In the absence of better scientifically valid sources of data, these remain the best estimates based on current scientific knowledge.

The study discarded numerous agents for which some scientific literature suggests that they are carcinogenic in humans. The basic rule is that only accumulation of scientific evidence from several sources (e.g., different independent scientific teams) and several disciplines (e.g., laboratory experiments and epidemiological data) can form the basis for a set of arguments consistent with the recognition of an agent as carcinogenic, or not carcinogenic, in humans.

Most studies on cancer risk factors were carried out in North America, the UK, the Nordic countries, the Netherlands, Italy or Asia. For many risk factors, no study has been conducted in France. This does not mean that relative risks derived from non-French studies are not valid for France, as toxic substances, drugs, pollutants, etc., are expected to exert similar effects in France and in other industrialized countries.

Weaknesses of this study reflect the currently inadequate knowledge in several fields, in particular:

1. The limited understanding of the complex processes involved in carcinogenesis (see Section E1).
2. The lack of reliable data on the causal association between many substances and cancer, bearing in mind that a statistical correlation between cancer and exposure to a substance does not imply causality.
3. Uncertainty about dose–effect relationships between exposure and cancer occurrence (see Section E1). The shape of the dose–effect relationship may be non-linear, e.g., an agent might be highly carcinogenic at high dose and innocuous at low dose.
4. The lack of availability of accurate data on exposure to known risk factors.
5. Differences in length of the lag-time for different carcinogens. For some factors, lag-time

may be very long (e.g., reproductive factors and breast cancer occurrence after 50 years old), but it may also be short, for instance benzene and leukaemia (about 5 years of lag-time).

Methodological limitations of the study

The methods we used for estimation of AFs may be criticized on several grounds:

(1) The lag-time of 15 years was somewhat arbitrary and exposures may have changed across generations. However, we adapted our choice of lag-time according to its relevance for risk factors. Thus, for instance, for hormone therapy and oral contraceptives, only current use was taken as relevant to breast cancer. For ultraviolet radiation and for professional exposure to asbestos, approaches for estimating AFs were not based on a lag-time.

(2) RRs and exposure measurements for AF calculations should be derived from similar populations having similar exposure to a specific risk factor. Since most of the RRs and data on exposure originated from different sources, the choice of RRs and exposures was sometimes not optimal (e.g., for physical inactivity).

(3) We assumed AFs to be equivalent for cancer incidence and mortality. This assumption is true only if the risk factor is not a prognostic factor for mortality, as the AF would then be different. For instance, obesity is a risk factor for breast cancer occurrence, but probably a stronger risk factor for breast cancer mortality after 50 years old. In this respect, the AF associated with obesity for breast cancer mortality is probably underestimated.

Difficulty in finding exposure data for France

We found exposure data for France for the majority of risk factors. However, we have to deplore the difficulty encountered in accessing many of the exposure data, despite the devoted efforts of the working group to identify potential sources. For some exposure prevalence data, reports or articles do not sufficiently describe the collection methods used and it therefore remains difficult to assess their quality. Many sources of data were not published in the scientific literature or in other peer-reviewed formats. This was particularly the case for data on occupational exposures. Great care was taken in choosing exposure data most representative of the prevailing situation in France at the end of the twentieth century. Data from certain sources were not used because they were derived from selected sub-populations unlikely to be representative of the French population. Exposure data doubtless exist of which we are unaware, but it is improbable that their availability would significantly change the estimates presented in this report.

In any case, this work has revealed the need for France to constitute a central repository of data on exposure prevalence, for instance, for the purpose of health surveillance. This repository should specify the methods used for data collection and be updated regularly.

How the study results can address public concerns about the "environment"

In the developed countries, exposure to known carcinogens has significantly decreased over time, mainly since the 1950s, as has exposure to many indicators of possible contact with carcinogens (e.g., some gases, "dirty" industrial activities, uncontrolled massive waste disposal). This historical fact in itself argues against the common perception that the "environment" is the cause of increases in cancer incidence.

For many exposures, there is not sufficient scientific evidence to establish them as cancer risk factors. In this respect, public concern about "environmental pollutants" is disproportionate to the known magnitude of impact of such pollutants on cancer. As stressed in the introduction to this report, some confusion comes from the different definitions for "environment", which has different meanings according to language. In their most appropriate sense, "environmental pollutants" include pollutants of water, air, soil and food.

Attribution of cancers with unknown cause to a single cause by default (or to a group of causes, e.g., "pollution") is unjustified and represents a fallacious argument. By similarly flawed reasoning, the gap in cancer causes could equally be attributed to global climate change, to the increasing number of televisions in our immediate environment, or to the

increase in social well-being.

It is unlikely that all cancers with 'unknown' cause are due to factors that will ever be identified. However, as seen in Sections A2, D3 and E1, even if we do not know the risk factor(s) responsible for the increasing incidence of a cancer, we usually do have clues as to the likely type of risk factor involved or not involved. In this respect, pollutants of air, food, water and soil, as well as occupational exposures, do not provide the preferred working hypotheses for the identification of risk factors responsible for the increase in incidence of some cancers. The development of new detection methods, screening effects, lifestyle factors, diet during pregnancy, infancy and childhood and hormonal and infectious agents are stronger avenues for future research.

Past studies on attributable risk of cancers

Several studies that estimated proportions of cancer attributable to risk factors were restricted to one risk factor or to one particular site of cancer (e.g., Mezzetti et al., 1998). Only four studies other than the present one estimated the impact of carcinogens on large populations and they used quite different methodologies (Doll and Peto, 1981; Olsen et al., 1997; Danaei et al., 2005; Doll and Peto, 2005). The main results of these studies are summarized in Table E2.1.

The first estimate of the relative importance of genetic and environmental factors in the global burden of cancer was made by Doll and Peto (1981) using cancer mortality data from the USA. In their seminal work, these authors came to the conclusion that around 80% of cancers could be attributable to a specific lifestyle or known environmental cause (Table E2.1). Subsequently, R. Peto and co-workers applied the same method to estimate the impact of tobacco smoking on the worldwide burden of cancer (Peto et al., 1994). Recently, J. Peto updated the estimates of the relative importance of causes of cancer for the world (Peto, 2001).

In 1981, Doll and Peto postulated that the greatest differences in cancer mortality between countries could reveal the pressure of environmental and lifestyle factors on cancer burden. Countries with the lowest rates for a specific cancer were more likely to reflect the background cancer rate essentially attributable to genetic or other endogenous factors. Their ranges of "acceptable estimates" (Table E2.1) were quite wide, reflecting uncertainties in the estimates. Thus, for instance, diet was deemed to account for 35% of cancer mortality, but the range of acceptable estimates was 10 to 70%. These estimates reflected the quality of the data available at that time. Furthermore, this methodology was implicitly based on the assumption that each type of cancer can be considered independently. This assumption is open to discussion. One factor, such as a high calorie intake through food, may increase the incidence of some cancers (directly or by increasing some hormonal secretions) and decrease the incidence of others (by enhancing the organism's defences). This is why it is useful to consider the overall impact of each risk factor. Another assumption was that non-genetic causes would sooner or later be identified for most common cancers. Nowadays, this assumption is no longer regarded as valid and it appears that the occurrence of many cancers is probably not associated with lifestyle or environmental causes (e.g., most prostate cancers) (see Section E1).

In 2005, Doll and Peto produced new estimates of the proportions of cancer deaths attributable to environmental and behavioural risk factors, this time for cancer deaths in the United Kingdom (Table E2.1). As for the 1981 report, the methods used to estimate AFs were not clearly detailed (e.g., sources of relative risks, exposure prevalence data, comparisons of cancer death rates in populations exposed and non-exposed to cancer risk factors). However, comparison of the figures reported in the two publications by Doll and Peto shows substantial changes in AF estimates for several factors, for instance diet. An accompanying note in the 2005 publication said that probably only 2% is avoidable in practice, mainly through avoidance of obesity. The AF for occupation was halved, probably to reflect changes in professional environments towards cleaner working places and less contact with hazardous substances.

Researchers from the Harvard School of Public Health (Danaei et al., 2005) attempted to determine the proportion of cancers attributable to lifestyle and environmental factors worldwide. These authors used estimates of relative risks derived from systematic reviews and meta-analyses. Exposure prevalences were estimated for each World Bank Region. For high-income countries, eight cancer risk factors were selected, and important risk factors such as

reproductive factors were not taken into account. Selection of exposure prevalence data did not always pick up the most appropriate and reliable sources in countries categorized as "high-income countries". The referent category for "no exposure" was chosen as the "theoretical minimum risk exposure distribution", an arbitrary category that seldom corresponds to real-world conditions. The authors concluded that the nine factors they selected accounted for about 43% of cancer deaths in high-resource countries in 2001.

The studies by Doll and Peto (1981, 2005) and by Danaei et al. (2005) were helpful for estimating the global effects of the main established causes of cancer. But these approaches were not always based on data on prevalence of exposure of populations (or of population subgroups) to known risk factors derived from, for instance, nationwide surveys or exposure monitoring. Furthermore, standard definitions of risk factors were not implemented across countries. Finally, the selection of risk factors in these studies was based on expert opinion rather than on attempts to systematically include all relevant cancer risk factors.

A study in the Nordic countries systematically examined prevalence of exposure to established risk factors in each Nordic country (Denmark, Finland, Iceland, Norway and Sweden) and then summed the estimates for all five countries, after weighting for population (Olsen et al., 1997). The relative risks used were derived from studies conducted in Nordic countries or, if no such study existed, from meta-analyses or the best available studies. In this respect, the methods used by the Nordic study resemble the approach we used for France. However, the Nordic study did not include several risk factors such as hormone replacement therapy, because in the mid 1990s the association between use of hormone replacement therapy and cancer had not yet been properly assessed by epidemiological studies or randomized trials. The same applies to physical inactivity.

Compared with similar previous work, our report provides new and more detailed information. Selection of risk factors was based on the best available knowledge of cancer risk factors in the year 2007 (and not on expert opinion), and exposure prevalences were derived from the most relevant French sources of data. However, further progress is still possible and relevant research is encouraged.

In spite of the different methodological approaches, many conclusions of the three studies based on selection of established cancer risk factors and estimates of prevalence of exposures (Olsen et al., 1997; Danaei et al., 2005; Tubiana et al., 2007) are consistent on several points:

(i) Tobacco smoking remains by far the main exogenous cancer risk factor, followed by alcohol drinking. The differences between the three studies on attributable fraction for tobacco are mainly due to differences in smoking prevalence between countries.

(ii) Two studies (Olsen et al., 1997; this study did not produce estimates of attributable fraction for dietary factors, and one (Danaei et al., 2005) just selected low intake of fruit and vegetables. As a result, at best only a marginal number of cancers, in the range of 0 to 3% were attributed to dietary factors.

(iii) The causes of large proportions of cancers are unknown and may be endogenous factors without significant impact of exogenous factors,

(iv) The impact of occupational risk factors is small and probably has diminished over recent decades; efforts should continue to further reduce this,

(v) Environmental pollution appears to be a relatively small risk factor. This does not mean that it should be neglected or overlooked. Rather, further fundamental and epidemiological research should be pursued on air, soil, food and water pollutants, with more thorough examination of defence against carcinogenesis and dose–carcinogenic effect relationships.

(vi) Finally, it appears that our knowledge on infectious factors (mainly viral) is insufficient.

References

Danaei G, Vander Hoorn S, Lopez AD, et al. Comparative Risk Assessment collaborating group (Cancers). Causes of cancer in the world: comparative risk assessment of nine behavioural and environmental risk factors. Lancet.

2005;366:1784-1793.

Doll R, Peto R. The causes of cancer: quantitative estimates of avoidable risks of cancer in the United States today. J Natl Cancer Inst 1981;66:1191-1308.

Doll R, Peto R. Epidemiology of cancer. In: Oxford Textbook of Medicine, 4th edition. Oxford, Oxford University Press, 2005.

Mezzetti M, La Vecchia C, Decarli A, et al. Population attributable risk for breast cancer: diet, nutrition, and physical exercise. J Natl Cancer Inst 1998;90:389–394

Olsen JH, Andersen A, Dreyer L, et al. Avoidable cancers in the Nordic countries. APMIS 1997;105, Suppl. 76.

Peto J. Cancer epidemiology in the last century and the next decade. Nature 2001;411:390-395.

Peto R, Lopez AD, Boreham J, et al. Mortality from Tobacco in Developed Countries, 1950-2000. Oxford, Oxford University Press, 1994.

Table E2.1 - Number of cancer cases or of cancer deaths and proportions attributed to various factors since the seminal work of R Doll and R Peto in 1981 *

	Doll and Peto, 1981, USA		Olsen et al, 1997, Nordic countries		Doll and Peto, 2005, UK		Danaei et al, 2005, high-income countries	This report		
Risk factors	% of cancer deaths	Range of estimates	% of cancer cases in men	% of cancer cases in women	% of cancer deaths	Range of estimates	% of cancer deaths	% of cancer deaths in men	% of cancer deaths in women	% of cancer deaths
Tobacco	30	25-40	19	9	30	27-33	29	33,4	9,6	23,9
Alcohol	3	2-4	2	1	6	4-8	4	9,4	3	6,9
Infectious agents	10?	1-?	2#	3#	5	4-15	<1.5 ∫	3,3	4,4	3,7
Diet	35	10-70	?§	?§	25	15-35	3 Ψ	NI	NI	NI
Obesity and overweight			<1	1			3	1,2	2,3	1,6
Physical inactivity			NI	NI	<1	0-1	2	0,5	3,2	1,6
Occupation	4	2-8	3	<1	2	1-5	NI	3,7	0,5	2,4
Pollutants	2	<1-5	<1 II	<1 II	2	1-5	NI	0.04	0,3	0,1
Urban air pollution			NI	NI			1	NI	NI	NI
Industrial products	<1†	<1-5	NI	NI	NI	NI	NI	NI	NI	NI
Food additives	<1	0.5-2	NI	NI	NI	NI	NI	NI	NI	NI
Medicines and medical procedures	1**	0.5-3	NI	NI	<1	0-1	NI	NI	NI	NI
Hormone replacement therapy and oral contraceptives			NI	NI			NI	NI	2,2	0,9
Reproductive factors	7 ϴ	1-13	NI	NI	15	10-20	NI	NI	1,1	0,4
Non-medical ionizing radiation	3‡	2-4	<1¶	<1¶	4	3-5	NI	NI	NI	NI
Ultraviolet light			4	5	1	1	NI	0,6	0,9	0,7
Man-made ionizing radiation	NI Я	NI	2	3	<1	<1-1	NI	NI	NI	NI

NI: factor not considered as being a cancer risk factor by the study - * Figures, ranges and «?» in the Table are as reported in the original publication
** Includes medical radiation, chemotherapeutic agents, oral contraceptives, hormone replacement therapy - † Includes numerous chemicals and physical agents introduced in daily life by modern industry
‡ Called «geophysical factors in Doll et Peto 1981», and included non-medical ionizing radiation and ultraviolet light
§ Authors considered that insufficient evidence existed for calculation of an attributable fraction - II Restricted to passive smoking - ¶ Restricted to radon - # Restricted to *H. pylori* infections
∫ Restricted to unsafe sex (1%) and contaminated injections in health-care settings (<0.5%) - Ψ Low fruit and vegetable intake - Я Included in the category «Medicines and medical procedures»
ϴ Includes sexual behaviours, i.e., infectious agents implicated in cancer of the cervix uteri

Section E3 : Recommendations

The conclusion that only a fraction of cancers occurring today in France is attributable to specific causes (and therefore is theoretically preventable) stresses the limitations of current knowledge on human carcinogenesis. While it is expected that in the future the evidence in favor or against a role of other risk factors will accumulate and eventually contribute to elucidating their contribution to human cancer, recommendations can be formulated to improve this process.

1. Recommendations to the scientific community

1.1 There is a need for large-scale, long-term prospective studies on exogenous and endogenous risk factors of cancer and other chronic diseases, with repeated measurements of relevant exposures. While the establishment and conduct of such studies exceed the resources of individual research groups, the medical research community should be encouraged to coordinate itself towards this goal. Links should be fostered between epidemiological and biological research. In the design and interpretation of epidemiological studies, more cooperation is recommended between epidemiologists, biologists, and clinicians. Cancer registries should be better used for cancer research; they should be encouraged to collect data regarding tumour characteristics as well as basic information (e.g., occupation) on the patients.

1.2 More attention should be paid to the assessment of pre- and peri-natal exposures, and of those occurring in infancy, childhood and adolescence. Ideally, the effects of these exposures should be studied within the framework of prospective studies (see recommendation 1.1); development of intermediate markers of risk might reduce the need for long-term follow-up.

1.3 The areas of cancer research which should be given the highest priority to improve the current understanding of the causes of human cancers – and the ability to prevent them – are those on nutrition, hormones, and infectious agents. The key contribution is likely to come from the development and validation of sensitive and specific methods of exposure assessment, including biomarkers, to be applied to large-scale population studies. Intervention studies would also provide critical evidence in the field of nutrition and cancer.

1.4 For known and suspected carcinogens, priority should be given to research (based on both epidemiological or biomarker approaches) aimed at analyzing defenses against mutation at the cellular level and against mutant cells at the tissue and organism levels.

1.5 In reviewing and quantifying the contribution of different causes to human cancers, more weight should be given to evidence-based summaries of the available data, than to the results of individual studies. The highest degree of scientific rigor and consistency should be applied to the assessment of available data. In general, conservative estimates are preferable to inferences based on weak evidence. Conflicts of interest of reviewers should be declared.

1.6 Publication bias should be avoided. A registry of all epidemiological studies (or at least all long-term prospective studies) should be set up and all results (positive or negative) should be collected. Leading journals should accept the publication of only studies which have been registered.

2. Recommendations to the administration and national or international research foundations

2.1 Ambitious long term studies should be encouraged. In particular, cohort studies should be set up, following individuals from the beginning of their life in utero to 50 or 60 years old in order to better understand the factors which influence health.

2.2 Data on cancer incidence should be collected from cancer registries, checked and made available to the research community in a timely manner. In normal circumstances, a delay of more than three years should not be accepted. In France, in the context of the 2003-2007 Cancer Plan, the surveillance system of the population has been improved, involving several institutions such as InVS, INSERM, AFFSET, INCa which are in charge of the collection and interpretation of data. Strong cooperation between these agencies is recommended in order to set up a database that would be constantly and rapidly updated and which would facilitate multidisciplinary research at the national, European and international level.

2.3 Large-scale, high-quality cross-sectional studies should be promoted to assess exposure to known and suspected cancer risk factors. Such surveys should be repeated at regular intervals. If already in place, these surveys should be coordinated and their results made easily accessible to the research community.

2.4 Priority should be given to the support of large-scale, prospective studies of cancer risk factors (see recommendations 1.1 and 2.1). Novel funding mechanisms might be taken in consideration to support such long term projects.

3. Recommendations regarding the information to the general public and the media

3.1 Emphasis should be given to comprehensive and evidence-based reviews of the evidence on the causes of human cancers. Evaluations made by international, multi-disciplinary panels should be given more weight.

3.2 Specific aspects of cancer risks and determinants (e.g., one particular cancer, one subset of the population, one risk factor) should be considered in a general perspective (e.g., mortality from all cancers, major risk factors) rather than in isolation. The role of chance and bias in generating false positive and false negative results should be given proper consideration.

3.3 The general public should be educated to cancer risk assessment and management. In particular, it is important that lay individuals acquire the ability to critically evaluate results on cancer risk factors. Health education at school offers the greatest opportunity for such educational efforts.