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).

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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.

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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

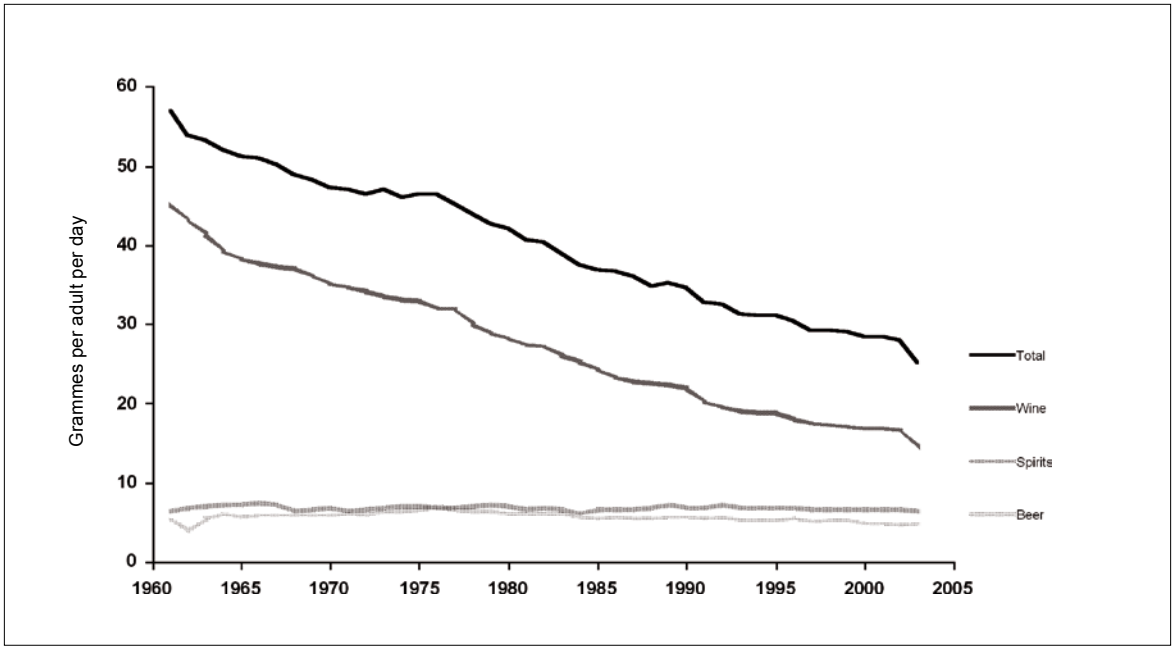


Fig. B2.2 - INRA/ONIVINS surveys on wine consumption in France (ONIVINS 2000)

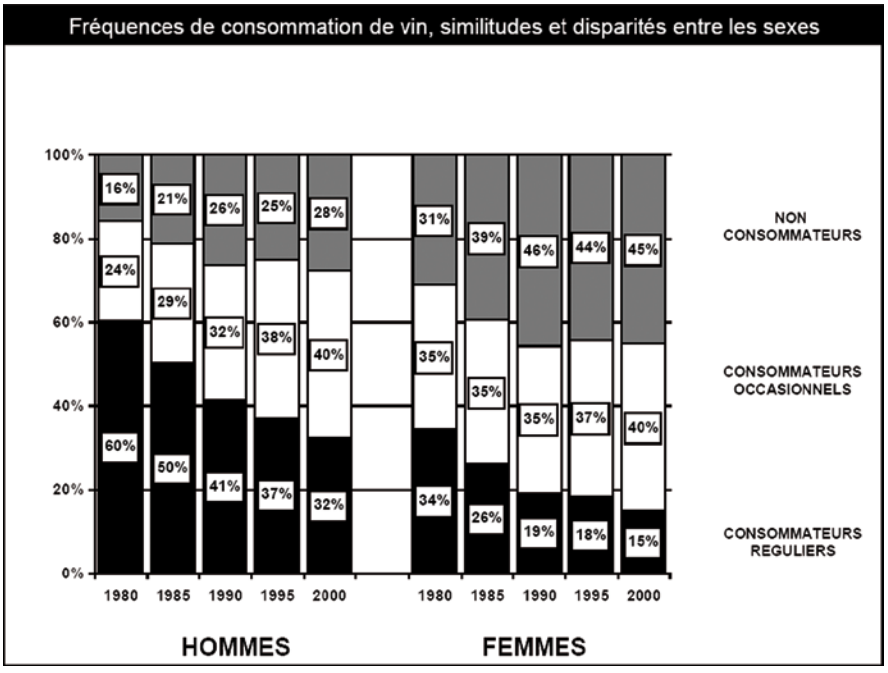


Figure B2.3 Mortality from liver cirrhosis in France
Data sources : INED and WHO Europe (* European standard population was used for rate calculations)

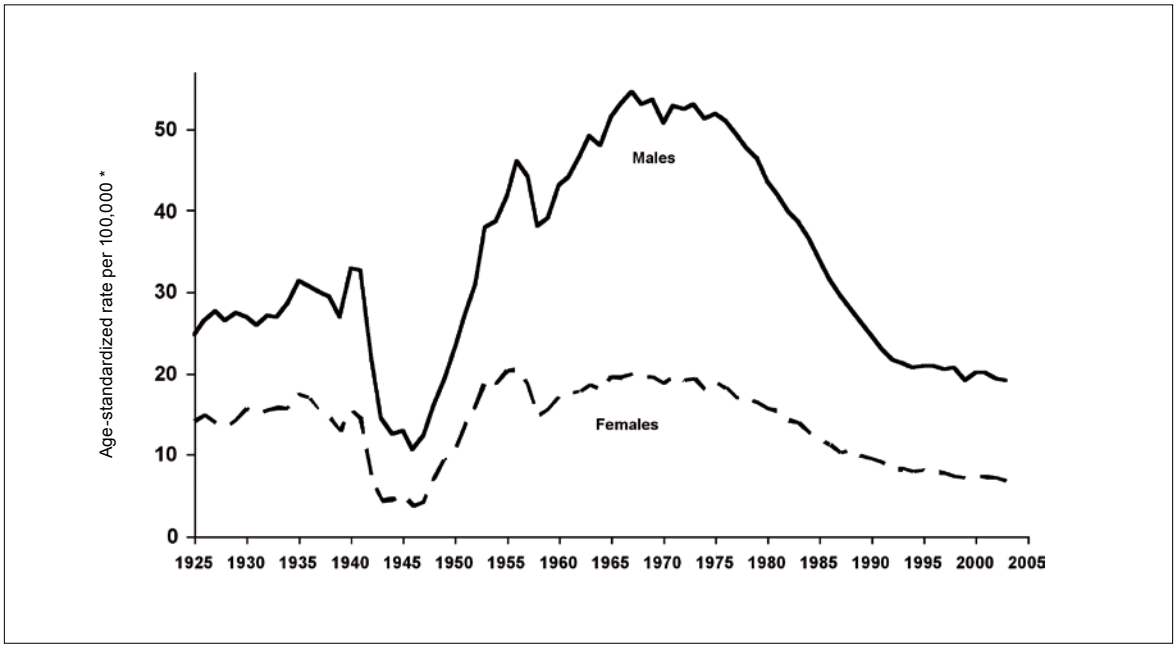
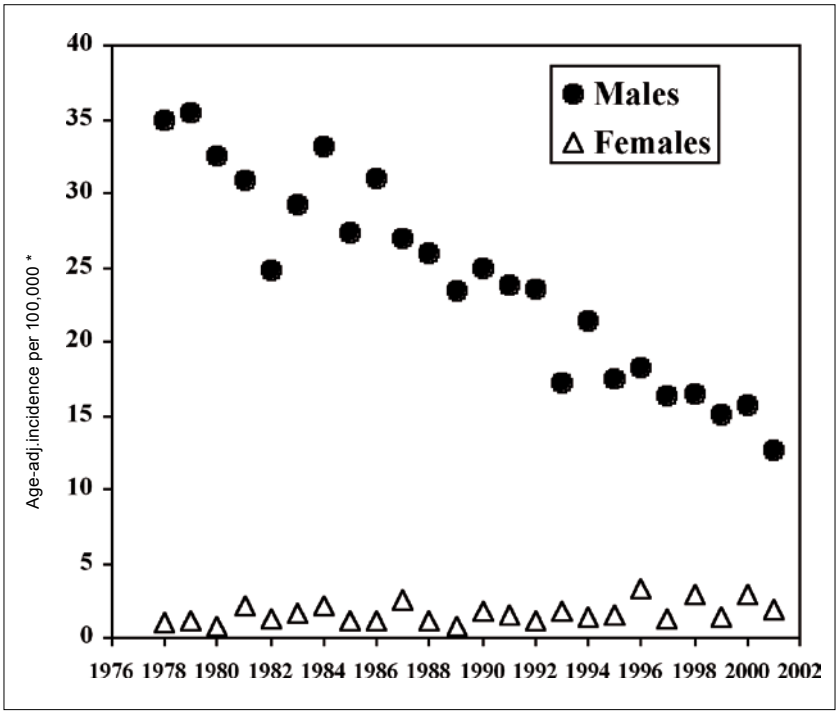


Figure B2.4 - Incidence of oesophagus cancer in Calvados. Incidence per 100 000 person-years, age-adjusted (world population). Data from Launoy et al. (1997), updated by G. Launoy for the needs of this study



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.

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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.

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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.

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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)

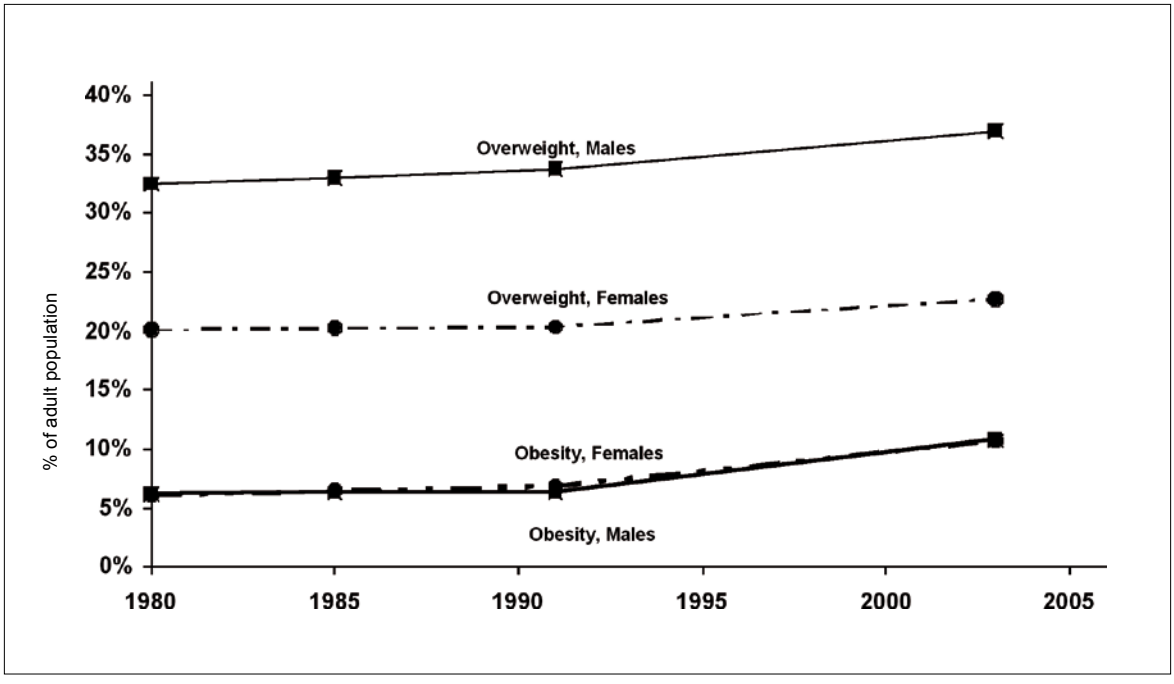
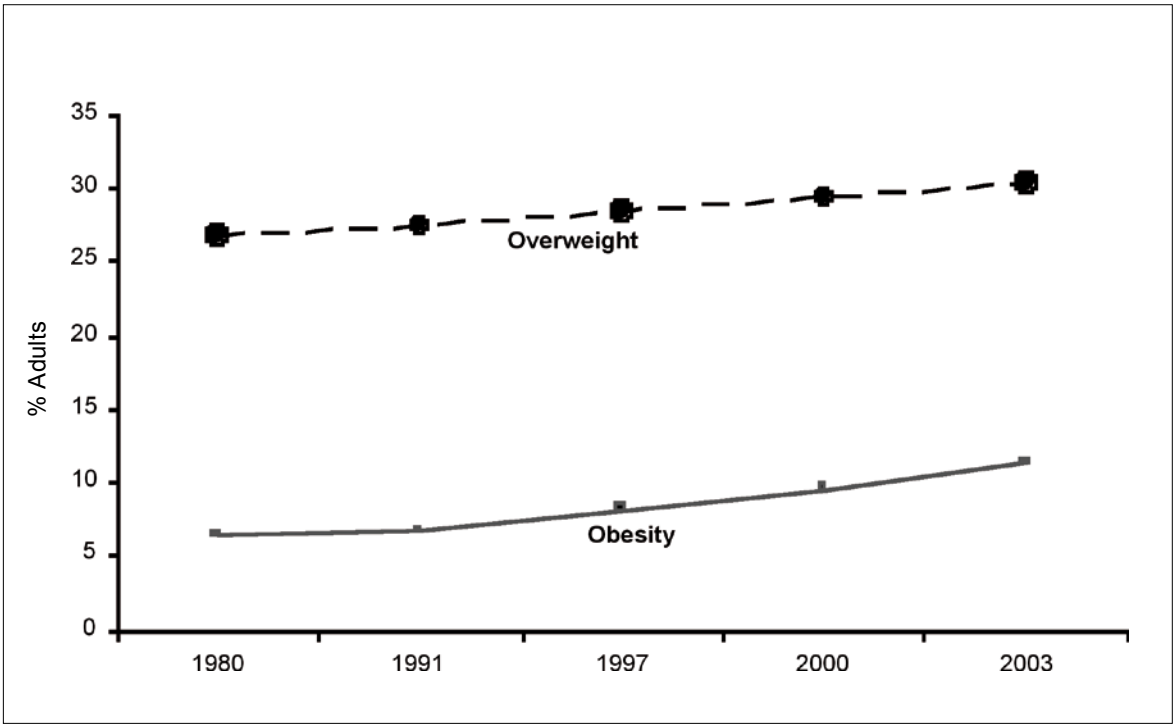


Figure B5.2 – Prevalence of overweight (BMI: 25-29.9) and obesity (BMI: 30+) in France in both sexes
(Data for 1980 and 1991 from INSEE, compiled by Maillard et al, 1999; data for 1997, 2000 and 2003 from ObEPI surveys, Charles et al., 2002 and ObEPI 2003)



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.

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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

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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

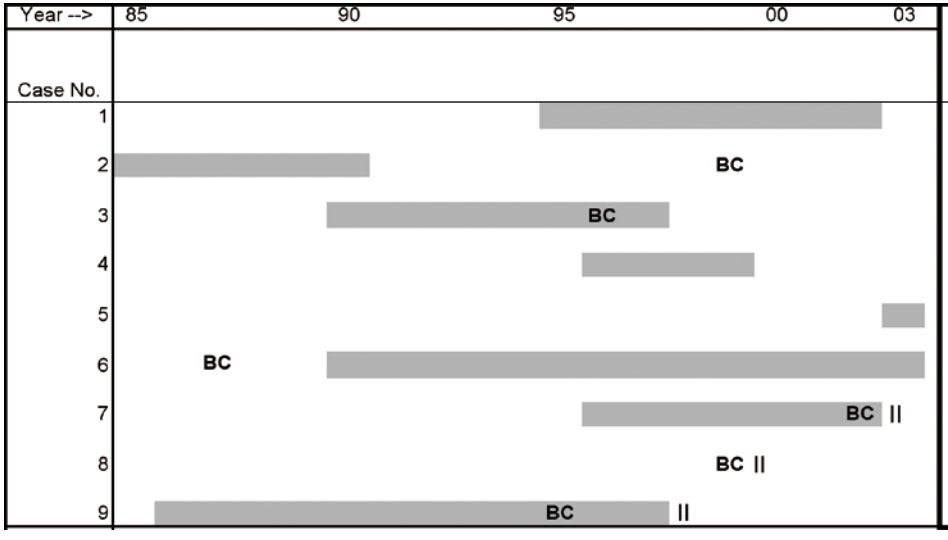
* Adjusted on age, BMI, follow-up time, and age at menopause

† 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).

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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.

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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)

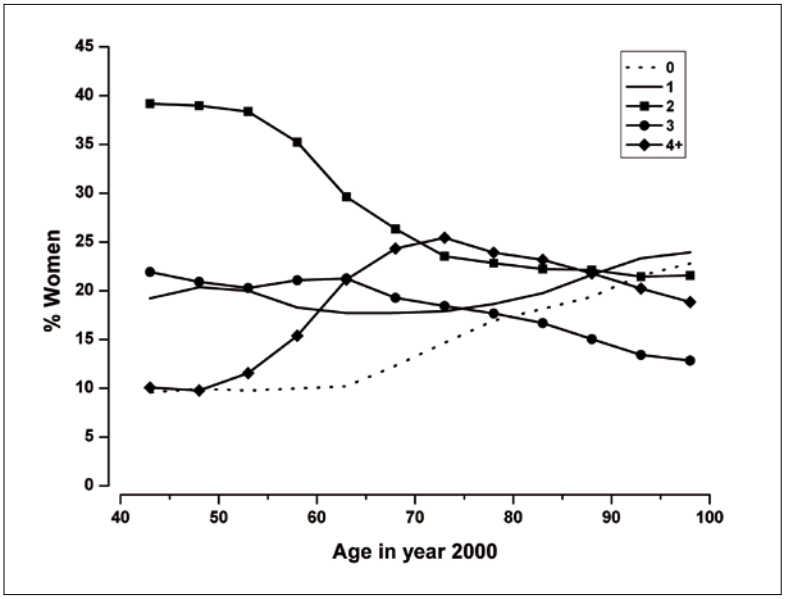


Figure B9.2 – Mean number of children per French woman 38 years old and more according to birth cohort
(estimated using data from INED)

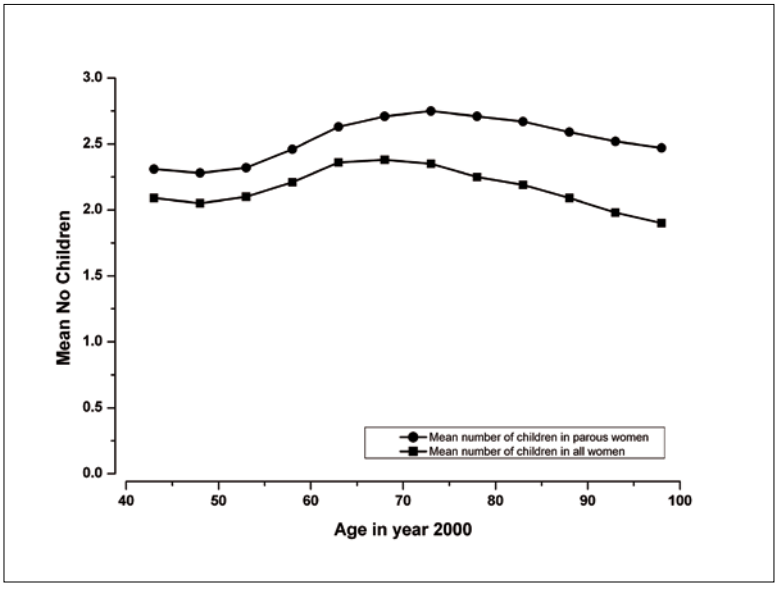


Figure B9.3 – Proportion of French parous women who had their first child at 30 years old more (data from INED)

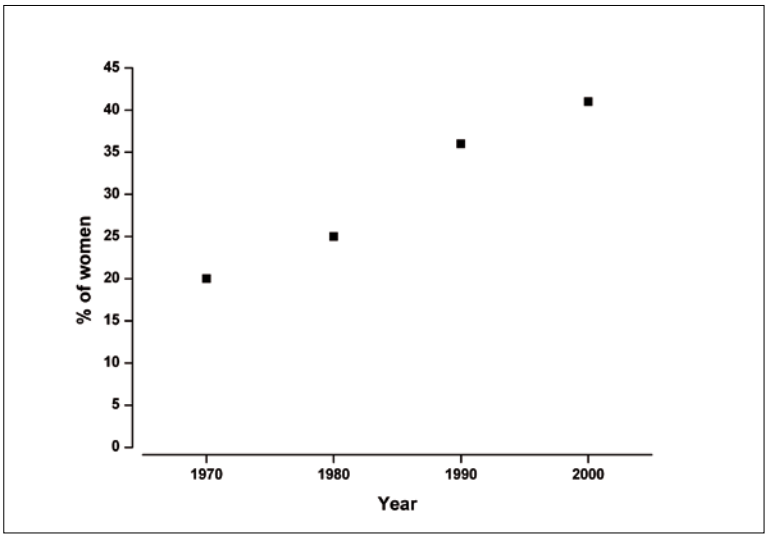
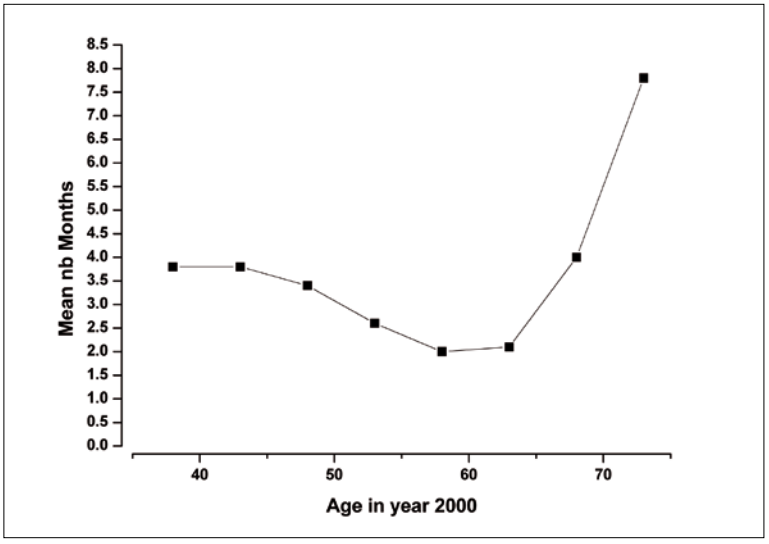


Figure B9.4 – Estimated mean number of months of breast feeding of parous women in France according to age in year 2000 (see text for data sources)**. Means are calculated considering all children women had.**



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.

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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