2.3 Synergistic carcinogenic effects of tobacco smoke and other carcinogens

2.3.1 *Introduction*

This section addresses the combined effects on cancer risk of cigarette smoking and other agents also associated with risk, excluding smokeless tobacco. The chapter is restricted to studies of smoking and exposures to single agents and does not address modification of risk by diet, whether by specific foods, nutrients or micronutrients.

For many cancers, including lung cancer, multiple causal factors are relevant and persons being exposed to more than one risk factor may be subject to risks beyond those anticipated from the individual agents acting alone. The terminology and methods used to characterize the combined effects of two or more agents have been poorly standardized with substantial blurring of concepts derived from toxicology, biostatistics and epidemiology (Greenland, 1993; Mauderly, 1993). Epidemiologists refer to *effect modification* if effects of multiple agents are interdependent whereas toxicologists assess whether the effects of multiple agents are *synergistic* (positive interdependence) or *antagonistic* (negative interdependence). Statisticians test whether there is *interaction* between independent determinants of cancer risk. For the purposes of this report, epidemiological concepts are followed, such that interdependence of effects is termed *effect modification*, and *synergism* and *antagonism* are used to describe the consequences of the interdependence of disease risk when both risk factors are present (Rothman & Greenland, 1998). The term *interaction* is reserved for the statistical approach for testing whether effect modification is present.

In a toxicological paradigm that extends from exposure through dose and finally to biological effects, there are a number of different points at which smoking might influence the effect of another risk factor. The 1985 Report of the US Surgeon General (US Department of Health and Human Services, 1985) set out a broad conceptual framework for considering the joint effect of smoking with an occupational agent, which can be extended more generally to other risk factors. The levels of potential interaction between agents are multiple, ranging from molecular to behavioural (Table 2.3.1). Current research on the molecular basis of carcinogenesis is improving the understanding of potential points of interaction at the mechanistic level, but approaches to assess effect modification remain largely empirical. Some of the potential points of interaction (Table 2.3.1) would have an impact on the level of exposure, others — including the exposure–dose relationship — on the dose–response relation of exposure with risk, either for smoking or for the modifying factor. Typically, epidemiological data do not provide evidence relevant for assessing each of these potential points of interaction of another risk factor with cigarette smoking. In assessing the presence of synergism or antagonism, a model is assumed to predict the combined effect from the individual effects; in the absence of sufficient biological understanding to be certain of the most appropriate model, the choice is often driven by convention or convenience. There is also a potential for the combined effects to vary over the life-span; as the carcinogenesis

process advances, agents are cleared (e.g. chrysotile asbestos fibres are cleared or dissolve in the lung), or exposure to tobacco or the other agent ends. Epidemiological studies generally only capture combined effects over a single interval of time.

In a multi-stage formulation of carcinogenesis, inferences as to the stages at which agents act can be made based on patterns of effect modification, particularly if data are available on the timing of exposure (Doll, 1971; Whittemore, 1977; Thomas & Whittemore, 1988). Effect modification also has implications for prevention, as synergism may increase the disease burden beyond that anticipated from the risk of smoking alone and may place some people, e.g. occupationally exposed workers, at particularly high risk.

The identification of studies addressing effect modification is difficult as authors may not have noted that effect modification was examined and search terms are not sufficiently conclusive. It was also impossible to search all studies involving smoking and potential modifying factors. Consequently, targeted searches were used to find published articles that specifically mentioned interaction, synergism or antagonism. Summary reviews also could be used as a further source of references.

(*a*) *Epidemiological concepts*

The effect of a risk factor for a disease may be estimated on an absolute scale or on a relative scale. In the absolute risk model, the risk ($r(x)$) of disease associated with some factor (x) can be expressed in a simple linear relationship as:

$$r(x) = r_0 + \beta x$$

while in a relative risk relationship, risk is given by:

$$r(x) = r_0 \times (1 + \beta x) = r_0 + r_0 \beta x$$

where r_0 is the background rate of disease in the absence of exposure and β describes the increment in risk per unit increment in exposure to x. Under a relative risk characterization of disease risk, the impact of an exposure on disease risk, $r_0 \beta x$, depends on the background rate. In the absolute risk model, the effect of exposure on disease risk, βx, does not depend on the level of r_0. The selection of the risk model (i.e. absolute or relative), has substantial implications for interpreting the combined effects of two agents and for extending risks observed in one population to another population that may not have comparable r_0 because of differing patterns of risk factors other than the exposure of interest.

These two models can be extended to address the effects of multiple causes of disease. In the example of two exposures, x_1 and x_2 (e.g. radon and smoking), disease risk ($r(x_1,x_2)$) under a relative risk model is given by:

Additive model: $r(x_1,x_2) = r_0 + r_0\beta_1 x_1 + r_0\beta_2 x_2$

Multiplicative model: $r(x_1,x_2) = r_0 \times (1 + \beta_1 x_1)(1 + \beta_2 x_2) =$

$r_0 + r_0\beta_1 x_1 + r_0\beta_2 x_2 + r_0\beta_1 x_1\beta_2 x_2 =$

$r_0 + r_0\beta_1 x_1 + r_0\beta_2 x_2(1 + \beta_1 x_1)$

Comparison of these two models highlights the differing dependence of the effect of x_2 on r_0 and x_1. In assessing the role of x_2 on disease risk, a multiplicative model implies that the effect of x_2 on disease risk depends not only on r_0, but also on the effect of x_1. In contrast, under the additive model, the effect of x_2 depends on r_0 but not on the effect of x_1.

Epidemiologists describe the effect of exposures in causing disease either as a difference on an absolute scale or as a ratio on a relative scale. The preference has been for ratio measures (e.g. the relative risk that compares risk in the exposed group to risk in a referent group, typically the unexposed group). Effect modification is considered to occur when the combined effect of two or more variables is larger or smaller than the anticipated effect predicted by the independent effects, based on the measure used (Greenland, 1993). Current analytical approaches compare the combined effect to predictions based on either additivity or multiplicativity of the individual effects, that is, using either the absolute risk or relative risk models described above. Thus, a factor may be an effect modifier in the additive model and not in the multiplicative model. Epidemiologists have recognized that the appropriate scale for assessing a combined effect depends on the intent of the analysis (Rothman *et al.*, 1980). For public health purposes, an effect greater than additive is considered as synergistic. Biological mechanisms, if sufficiently understood, may suggest an alternative scale for assessment.

Although epidemiological methods have been proposed for assessing effect modification, no strict criteria for determining its presence have been defined. Rothman (1976) developed a synergy index that quantifies departure from independence of effects. Statistical significance alone is recognized to be an insufficient criterion (Greenland, 1993), and the interpretation of patterns of interdependence remains subjective. Additionally, inadequate statistical power often limits the assessment of effect modification (Greenland, 1983) and interpretation of possible effect modification should also consider the consequences of exposure measurement error, which may differ in degree for smoking and the other agent(s).

The concern about limited power extends specifically to studies of smoking and disease. Particularly limiting is the small number of cases that occur among nonsmokers in the studies of occupational agents.

(*b*) *Statistical concepts*

Statisticians have used the term ‘interaction’ to refer to interdependence as detected by a statistical approach or ‘model’. Interaction, which is equivalent to the epidemiological concept of effect modification, has typically been assessed in a regression framework using product terms of the risk factors of interest to test for effect modification (Thomas & Whittemore, 1988; Rothman & Greenland, 1998). For example, interaction between two risk factors, x_1 (e.g. smoking) and x_2 (e.g. radon exposure) could be assessed using the following model:

$$r(x_1, x_2) = 1 + \beta_1 x_1 + \beta_2 x_2 + \beta_3 x_1 x_2$$

In this linear model, the product or interaction term, $\beta_3 x_1 x_2$, estimates the joint contribution of the two agents to the risk. The model provides an estimate of the value of β_3 and a test of the statistical significance of β_3 for the null hypothesis: $\beta_3 = 0$. This modelling approach inherently assumes a mathematical scale on which the interaction is characterized, the usual choices being additive or multiplicative. Most often, primarily because of computational convenience, the multiplicative scale is used. Alternative approaches for assessing interaction have been described (Thomas, 1981; Breslow & Storer, 1985; Lubin & Gaffey, 1988). These choices more flexibly estimate the combined effects of risk factors without imposing the rigidity of a particular scale. Imprecision and bias from measurement error may also limit estimates obtained from such modelling approaches.

(*c*) *Characterizing the burden of cancer attributable to smoking*

In describing the burden of disease, epidemiologists use a quantity referred to as the attributable risk (Rothman & Greenland, 1998). The attributable risk indicates the burden of disease that could be avoided if exposure to the agent of concern were fully prevented. This measure has been widely used for cigarette smoking to estimate the burden of avoidable tobacco-caused disease.

One form of the attributable risk, the population attributable risk (PAR) describes the proportion of disease in a population associated with exposure to an agent. For a factor, x_1, having an associated relative risk RR_1, PAR is calculated as below, where I and I_0 and P_1 and P_0 are the disease rates and probabilities of exposure in the population under current conditions and under some counterfactual set of conditions of differing exposure (for smoking, generally the complete prevention of smoking), respectively:

$$\begin{aligned} PAR(x) &= \frac{I - I_0}{I} \\ &= \frac{P_1 I_1 + P_0 I_0 - I_0}{P_1 I_1 + P_0 I_0} \\ &= \frac{P_1(RR_1 - 1)}{P_1(RR_1 - 1) + 1} \end{aligned}$$

For diseases caused by several agents, the total burden of disease that is theoretically preventable may exceed the observed number of cases, or 100%, if there are synergistic patterns of effect modification on an additive scale. For example, an estimate of smoking-attributable lung cancer cases can be conceptualized as including those cases caused by smoking, and those caused by radon and smoking in smokers. In the above formula, the attributable risk figure for smoking includes those cases caused by smoking alone and radon and smoking acting together; similarly, the attributable risk figure for radon would include those cases caused by radon alone and those caused by radon acting together with smoking. Combining the attributable risk estimates for smoking and radon counts the jointly determined cases twice. This subtlety of the attributable risk statistic is not uni-

versally appreciated and there is widespread misperception that the attributable risk should add up to 100% when all the various causes of the cancer are considered.

For two factors, x_1 and x_2, the sum of the individual exposure-specific PAR estimates, PAR(x_1) and PAR(x_2), can exceed 100%. However, when evaluating two factors, these PARs are incorrectly determined by contamination of the referent groups; i.e. the subgroup of individuals with $x_1 = 0$ includes subjects for whom x_2 may be 0 or 1 and the subgroup of individuals with $x_2 = 0$ includes persons for whom x_1 may be 0 or 1.

For joint exposures to x_1 and x_2, PAR is defined as:

$$\mathrm{PAR}_{(x1,x2)} = \frac{P_{1,1}(\mathrm{RR}_{1,1} - 1) + P_{1,0}(\mathrm{RR}_{1,0} - 1) + P_{0,1}(\mathrm{RR}_{0,1} - 1)}{P_{1,1}(\mathrm{RR}_{1,1} - 1) + P_{1,0}(\mathrm{RR}_{1,0} - 1) + P_{0,1}(\mathrm{RR}_{0,1} - 1) + 1}$$

The PAR for two exposures, e.g. smoking and radon, is the sum of components due to smoking in the absence of radon exposure, to radon exposure in the absence of smoking, i.e. in never-smokers, and to the combined effect of radon exposure and smoking. PAR(x_1,x_2), calculated with the above formula, cannot exceed 100%.

Finally, the definition of PAR can be generalized for a continuous exposure, x, with exposure distribution f, as

$$\begin{aligned}\mathrm{PAR(x)} &= \frac{I - I_0}{I} \\ &= \frac{\int I(\mathrm{x})\mathrm{f}(\mathrm{x})\mathrm{dx} - I_0}{\int I(\mathrm{x})\mathrm{f}(\mathrm{x})\mathrm{dx}} \\ &= \frac{\int \mathrm{RR}(\mathrm{x})\mathrm{f}(\mathrm{x})\mathrm{dx} - 1}{\int \mathrm{RR}(\mathrm{x})\mathrm{f}(\mathrm{x})\mathrm{dx}}\end{aligned}$$

where RR(x) is the relative risk for exposure level x, relative to zero exposure.

2.3.2 *Asbestos*

Asbestos, a term referring to a group of fibrous silicates, has long been identified as a cause of lung cancer, and was classified by IARC as *carcinogenic to humans* (Group 1) (IARC, 1987). Many studies of asbestos-exposed workers have addressed the combined effect of asbestos and smoking on lung cancer risk. Data available at the time allowed the Working Group to establish that 'the relationship between asbestos exposure and smoking indicated a synergistic effect of smoking with regard to lung cancer' (IARC, 1987). There have been several recent comprehensive reviews on this topic (Erren *et al.*, 1999; Lee, 2001; Liddell, 2001), as well as several frequently-cited earlier reviews (Saracci, 1977; Vainio & Boffetta, 1994). The topic has also been addressed in several reviews on occupational carcinogens in general and smoking (Saracci, 1987; Saracci & Boffetta, 1994).

Tables 2.3.2 and 2.3.3 summarize the characteristics of the principal relevant case–control and cohort studies, respectively, reviewed by Lee (2001), together with one more recent study (Gustavsson *et al.*, 2002). These studies vary widely in design and in the quality and extent of information available on smoking and on asbestos exposure. In the cohort studies, exposure to asbestos was generally at levels that would be considered high in relation to today's occupational standards. Exposure estimates were based on available sources of information including measurements that were generally limited in scope. Types of information included: job and industry, judgement of industrial hygienists, and self-report. The extent of the available information on smoking was also variable and in many of the cohort studies information was collected only at the initiation of follow-up or some other single point in time. In the case–control studies, interviews with the participants or with a surrogate respondent for deceased persons were the principal source of information.

Tables 2.3.4 and 2.3.5, adapted from Lee (2001), provide the relative risks for the four strata created by dichotomous classification of smoking and asbestos exposure. The general pattern of the risk estimates indicated departure from additivity in many of the studies, although the findings of some studies did not indicate synergism (McDonald *et al.*, 1993; McDonald *et al.*, 1999). The extent of departure from additivity varied across studies, from only slightly greater than additive (Gustavsson *et al.*, 2002) to a multiplicative interaction (Hammond *et al.*, 1979).

The three recent reviews include quantitative summaries of the evidence on effect modification. [The Working Group did not attempt to replicate these analyses.]

Erren and colleagues (Erren *et al.*, 1999) identified 17 relevant reports published from 1966 to 1996. Of these, 12 were included in the analysis, which used Rothman's synergy index. The value of the synergy index exceeded unity in all of the 12 studies. After excluding one study and verifying the absence of significant heterogeneity between the studies, the weighted summary value of the synergy index was estimated as 1.66 (95% CI, 1.33–2.06).

Liddell (2001) focused on seven cohort studies and six case–control studies. He also calculated an index of effect modification, termed the relative asbestos effect (RAE), which exceeded unity if the effect was greater in nonsmokers than in smokers. For the cohort studies, the estimate of RAE was 2.04 (95% CI, 1.28–3.25), indicating that the relative risk for asbestos exposure in nonsmokers was twice that in smokers; for the case–control studies, the RAE estimate was 0.83 (95% CI, 0.53–1.30). Liddell set aside the case–control data as being of insufficient quality and found that the data from cohort studies were not consistent with a fully multiplicative interaction. [The Working group noted that Liddell did not test for departure from additivity].

Lee (2001) analysed data from 23 studies, testing for additivity and multiplicativity. The studies reviewed showed strong evidence for departure from additivity. A test of multiplicativity was used that was conceptually comparable to Rothman's synergy index. Although the value of this index varied substantially across studies, the summary value of

the synergy index derived by meta-analysis was 0.90 (95% CI, 0.67–1.20), which was consistent with a multiplicative interaction.

The discrepancy between the analyses, findings and conclusions of Erren *et al.* (1999), Lee (2001) and Liddell (2001) lies in the selection of studies and the approaches used to abstract and analyse the evidence. All three reviews document the range of the evidence and the imprecision with which many of the studies assess effect modification.

The Working Group concluded that the evidence supports synergism between asbestos exposure and smoking in causing lung cancer, but notes that the degree of synergism remains uncertain.

2.3.3 *Radon and other ionizing radiation*

The combined effect of radon and smoking has been investigated in cohort studies of underground miners exposed to radon and radon progeny and in case–control studies of lung cancer and exposure to radon in homes. The Working Group for the *IARC Monograph* on radon 'considered that the epidemiological evidence [did] not lead to a firm conclusion concerning the interaction between exposure to radon decay products and tobacco smoking' (IARC, 1988a). The report of the US National Research Council's Biological Effects of Ionizing Radiation (BEIR) VI Committee provided an in-depth review of the combined effect of smoking and radon on lung cancer risk and the following section is largely based on this report (National Research Council, 1999). The cohort and case–control studies cited in that review, together with more recent studies, are included in Tables 2.3.6 and 2.3.7.

The BEIR VI Committee identified five cohort studies of underground miners that provided information on both smoking and exposure to radon progeny (Table 2.3.6). The extent of information available on smoking was variable and smoking was not systematically evaluated across the follow-up of any of the cohorts. Quantitative estimates of exposure to radon progeny were available for all participants. The data had been analysed by Lubin *et al.* (1994) using a mixture model that flexibly assessed effect modification. The two largest studies, the study of Colorado Plateau uranium miners and the study of Chinese tin miners, provided the strongest evidence of effect modification because of the size of the cohorts and the numbers of lung cancer deaths. Both studies provided evidence against the additive model, as did the overall estimate for the mixture parameter, which indicated a synergistic but submultiplicative interaction.

In modelling the risk for lung cancer, the BEIR VI Committee adopted this submultiplicative interaction. Relative to the overall effect of exposure to radon progeny on lung cancer risk, the risk estimate in ever-smokers was proportionally lower by a factor of 0.9 whereas the relative effect in never-smokers was proportionally higher by 1.9.

Hornung and colleagues (Hornung *et al.*, 1998) reported an analysis of the Colorado Plateau study that incorporated updated smoking information obtained in 1986 from surviving cohort members and next of kin of deceased members. The smoking histories, updated for about two-thirds of the original cohort, showed a substantial rise in the

proportion of former smokers. Multiple analytical approaches were used to explore effect modification. The general finding was that the interaction between smoking and radon was submultiplicative, but there was no strong evidence against a multiplicative interaction.

Further evidence on smoking and exposure to radon progeny has come from a population-based case–control study conducted in Gejiu City, the site of the Yunnan Tin Corporation (Yao *et al.*, 1994). This study included 460 cases, of whom 368 had been miners, and 1043 controls. Tobacco was smoked by study participants as cigarettes or with water pipes or Chinese long-stem pipes; a mixed pattern of smoking was most common. In contrast to the cohort analysis of the Yunnan tin miners, the case–control data were consistent with a multiplicative model, although the best-fitting model was intermediate between additive and multiplicative.

The joint effect of smoking and exposure to radon progeny could plausibly vary with the sequence of the two exposures. Thomas and colleagues (Thomas *et al.*, 1994) analysed the Colorado Plateau data using a case–control approach to assess temporal modification of the interaction between radon progeny and smoking. They characterized the temporal sequence of the two exposures as: simultaneous; radon before smoking; and radon following smoking. Exposure to radon followed by smoking was associated with an essentially additive effect whereas smoking followed by exposure to radon was associated with a more than multiplicative effect on a relative risk scale. Thomas and colleagues interpreted this finding as suggesting that smoking could act to promote radon-initiated cells.

The data from the Colorado Plateau cohort and Yunnan tin miners cohort have been analysed with mechanistic carcinogenic models, based in the Moolgavkar, Venzon and Knudson two-mutation model (Moolgavkar *et al.*, 1993; Luebeck *et al.*, 1999; Hazelton *et al.*, 2001; Little *et al.*, 2002). Under the assumed models, inferences can be made as to the mutations affected by smoking and exposure to radon progeny. In the most recent analysis of the Colorado Plateau cohort data (Little *et al.*, 2002), the findings of a two-stage model implied action of both factors on the first mutation rate and an action of exposure to radon progeny on intermediate cell death or the differentiation rate. A two-stage model was applied by Hazelton *et al.* (2001) to the Yunnan tin miner cohort data, which included estimates of exposure to smoking, arsenic and radon progeny. Various models were fitted; all showed effects of each of the exposures; radon had the smallest effect and smoking the greatest.

Effect modification has also been assessed in case–control studies of lung cancer in the general population (Table 2.3.7). All studies made estimates of radon concentration in the current and past homes of persons with lung cancer and of appropriate controls. Information on smoking was obtained by interview with the index respondent or with a surrogate for deceased persons. Measurement error is an unavoidable limitation of these studies, as exposure to radon throughout the lifetime is considered relevant to risk for lung cancer in adulthood.

Because most cases of lung cancer occur in smokers, the case–control studies included few never-smokers and consequently effect modification cannot be characterized with great precision. The available studies do not provide evidence for effect modification, considered

on the multiplicative scale. [The Working Group noted that the studies have not been systematically analysed for the presence of synergism, assessed as departure from additivity].

The combined effect of smoking and exposure to radiation has been assessed in a few populations exposed to low-linear energy transfer (LET) radiation. These populations included atomic bomb survivors (Prentice *et al.*, 1983; Kopecky *et al.*, 1986), persons receiving therapeutic irradiation for breast cancer (Kaldor *et al.*, 1992; Neugut *et al.*, 1994; Van Leeuwen *et al.*, 1995), and workers subjected to mixed exposure to external gamma radiation and internal emitters (Petersen *et al.*, 1990).

Of the cancer risks associated with exposure to radiation in atomic bomb survivors, relative risks for lung cancer are among the highest (Mabuchi *et al.*, 1991). A series of studies conducted by the Radiation Effects Research Foundation have explored the effect of smoking on lung cancer in the atomic bomb survivors. Kopecky *et al.* (1986) reported an analysis of the combined effects of smoking and radiation in a selected cohort for which information was available on smoking. A total of 351 cases of lung cancer were reported in a cohort of 29 332 exposed survivors. Poisson regression models were used to assess the effects of exposure to radiation (using the T65 radiation dosimetry), and smoking, with control for other factors including age at the time of the bombing. Using an additive model for the excess relative risk, Kopecky *et al.* (1986) found that both exposure to radiation and cigarette smoking were determinants of lung cancer risk; an interaction term for the two exposures was not statistically significant ($p = 0.72$). While Kopecky *et al.* (1986) expressed a preference for the additive model based on these analyses, further analyses by the BEIR IV Committee (National Research Council, 1988) showed that the data were equally compatible with a multiplicative model.

Three studies have examined modification by cigarette smoking of the risk for lung cancer following therapeutic irradiation.

Neugut *et al.* (1994) conducted a case–control study of Connecticut women with a second primary cancer following an initial diagnosis of breast cancer. The cases ($n = 94$) were women with lung cancer as the second primary cancer whereas the controls ($n = 598$) had a second malignancy of a type not associated with smoking or radiation. The pattern of the increased risk associated with both smoking and radiation therapy for the initial breast cancer was consistent with a multiplicative interaction; however, the consistency of the data with different models was not formally assessed.

Van Leeuwen *et al.* (1995) used a nested case–control design to assess risk for lung cancer in relation to radiation and smoking in a cohort of 1939 patients who had received treatment for Hodgkin disease in the Netherlands. The 30 cases identified during an 18-year follow-up were matched to 82 controls. Radiation doses to the region of the lung where the case developed cancer were estimated and information on smoking was obtained from several sources. There was a significantly greater increase in risk among smokers in relation to estimated radiation dose than among nonsmokers. However, in reviewing the findings, Boivin (1995) showed that the pattern of combined effects was consistent with additivity of the excess relative risks. This study was limited by the small number of lung cancer cases and by the potential modifying effects of chemotherapy.

Therapy for small-cell carcinoma of the lung includes aggressive chemotherapy and radiation. Tucker *et al.* (1997) carried out a multi-centre study in North America of 611 persons treated for small-cell carcinoma of the lung and who remained cancer-free for at least two years after the therapy. The risks varied with smoking status with the highest risk being found in those who continued to smoke after the initial diagnosis of lung cancer (relative risk = 21); no second lung cancers were observed in the 13 never-smokers. The authors reported that the interaction was not statistically significant when a model was used to assess interaction.

2.3.4 *Arsenic*

The combined effect of smoking and arsenic on lung cancer risk has been examined in occupational groups exposed to arsenic through work in smelting or metal mining. Table 2.3.8 summarizes the studies included in two relevant reviews (Hertz-Picciotto *et al.*, 1992; Saracci & Boffetta, 1994).

Hertz-Picciotto *et al.* (1992) used data from six studies (Rencher *et al.*, 1977; Pershagen *et al.*, 1981; Enterline, 1983; Pershagen, 1985; Enterline *et al.*, 1987; Järup & Pershagen, 1991) to evaluate the pattern of joint effects. Although the data available from the different studies were not uniform, the analysis indicated a pattern of combined effects that was consistently greater than additive.

2.3.5 *Alcohol drinking*

The combined effects of smoking and alcohol consumption on cancers of the oral cavity, pharynx, larynx and oesophagus have been examined extensively, and to a lesser degree for cancer of the liver (Table 2.3.9). The studies varied in their methods and in the approaches used to assess effect modification, which ranged from descriptive to formal estimation of interaction terms in multivariate models.

(*a*) *Cancers of the upper aerodigestive tract*

For cancers of the oral cavity and pharynx, the evidence comes entirely from case–control studies carried out in Asia, Australia, Europe and the United States. In the majority of the studies, evaluation of effect modification was descriptive, without formal assessment of interaction. Overall, however, the pattern of odds ratios for smoking, across categories of alcohol consumption, is consistent with synergism. In two studies with relatively large numbers of cases and controls, the pattern of increasing cancer risk with increasing alcohol consumption is strong (Mashberg *et al.*, 1993; Kabat *et al.*, 1994). In both studies, the pattern of odds ratios for men and women was consistent with synergism and a test for interaction was statistically significant for both sexes.

Seven case–control studies and one cohort study reported on joint effects of tobacco smoking and alcohol drinking on the risk for oesophageal cancer. Generally, the studies support a positive departure of joint effects from additivity. Since multiple logistic

regression models were used for analysing most of these studies, some also were tested for departure from multiplicativity. These tests for interaction are inadequate to assess synergy as defined in this monograph.

Most of the case–control studies of laryngeal cancer provide strong evidence for synergism. The studies were carried out in a number of locations around the world. Only the study in Shanghai (Zheng *et al.*, 1992) did not yield evidence consistent with synergism. In a number of studies, tests for interaction were carried out and reported to be 'non-significant.' These were tests for departure from the multiplicative models, typically multiple logistic regression models, used to analyze the case–control data, and not tests for departure from additivity.

Several studies reported on findings on cancer of the 'mixed upper aerodigestive tract', comprising studies of patients with squamous cell carcinomas, regardless of the specific site within the head and neck region. These studies also provided strong evidence for synergism.

(*b*) *Liver cancer*

Alcohol consumption is an established cause of liver cancer (IARC, 1988b) and of hepatic injury, which may lead to hepatic cirrhosis. Six case–control studies were identified that included information on the joint effect of smoking and alcohol consumption on liver cancer risk. In three studies, odds ratios for smokers were greater if they were also in the higher category of alcohol consumption (Chen *et al.*, 1991; Yu *et al.*, 1991; Kuper *et al.*, 2000). In one study (Kuper *et al.*, 2000), there was a statistically significant and super-multiplicative interaction between heavy smoking and heavy drinking in causing liver cancer.

2.3.6 *Infectious agents*

(*a*) *Hepatitis B*

Two case–control studies were identified that provided evidence on risk for liver cancer associated with smoking by serological status for hepatitis B infection (Table 2.3.10). The results are conflicting; the study conducted in Greece (Trichopoulos *et al.*, 1987) showed generally lower odds ratios in subjects who were seropositive for hepatitis B surface antigen compared with those who were negative for the antigen, whereas the study from China, Province of Taiwan (Chen *et al.*, 1991) showed greater risks in subjects who were positive for hepatitis B surface antigen.

(*b*) *Human papillomavirus*

For cervical cancer (squamous-cell type), evidence suggests that human papillomavirus (HPV) is a necessary factor, and implies that the risk of smoking cannot be estimated in the absence of HPV infection. Because the absolute risk of cervical cancer in the absence

of HPV infection, is hence by definition zero, the incremental risk associated with smoking is interpreted as indicating synergism (Table 2.3.11).

(*c*) Helicobacter pylori

A case–control study of stomach cancer in Moscow examined the combined effect of smoking and *H. pylori* infection (Zaridze *et al.*, 2000). In non-infected persons, the odds ratio, comparing ever- to never-smokers was 1.2 (95% CI, 0.8–1.8) whereas in infected persons, the odds ratio was 1.6 (95% CI, 1.0–2.4). The odds ratios did not vary significantly with infection status. No other studies were identified.

2.3.7 *Others*

(*a*) *Nickel*

Only one study addressed the combined effect of occupational exposure to nickel and cigarette smoking. Andersen and colleagues (Andersen *et al.*, 1996) reported the findings of a cohort study of workers (n = 4764) at the Falconbridge nickel refinery (Norway). Information on smoking was obtained primarily from medical records at the refinery and from co-workers. Assessment of effect modification was restricted to 1337 men who were in the same birth cohorts as a population comparison group. The results were consistent with a combined effect of nickel exposure and smoking that is multiplicative: the relative risk for unexposed smokers was 6.1; the relative risk for exposed never-smokers was 3.6; and relative risk for exposed smokers was 23.

(*b*) *Silica (silicon dioxide)*

Exposure to silica is common among miners, sand-blasters and many other occupational groups. Crystalline silica has been classified by IARC as *carcinogenic to humans* (Group 1) (IARC, 1997) and is also known to cause silicosis, a fibriotic disorder of the lungs. Workers with silicosis have an increased risk for lung cancer that may be the direct consequence of the silica particles deposited in the lung, or an indirect consequence of the lung fibrosis.

Studies that have investigated the combined effect of smoking with silica exposure are summarized in Table 2.3.12 (Saracci & Boffetta, 1994). Both studies on silica exposure and on silicosis were included. No consistent patterns of effect modification were evident in either group of studies.

(*c*) *Chloromethyl ethers*

The chloromethyl ethers include chloromethyl methyl ether and bis(chloromethyl)-ether; these compounds were used in the chemical industry as intermediates in organic synthesis and in the production of ion exchange resins. The strong association of exposure to this agent with lung cancer was first reported by Figueroa *et al.* (1973) who described 14 cases; three were in never-smokers and the histology for 13 of the cases showed that

only one was not a small-cell carcinoma. On follow-up of workers in the plant, nonsmokers were found to comprise a higher proportion of cases than in the general population (Weiss *et al.*, 1979). In a small cohort ($n = 51$) apparently drawn from the same plant (Weiss, 1980), the standardized mortality rate for lung cancer death was markedly higher for never-smokers and former smokers together, compared with current smokers. The authors interpreted this analysis as indicating antagonism between smoking and exposure to chloromethyl ethers. [The Working Group noted the limited information available on the joint effect of smoking and exposure to chloromethyl ethers.]

Table 2.3.1. Examples of levels of interaction between smoking and another agent

Exposure
• Work assignments of smokers and nonsmokers are different.
• Absenteism rates differ for smokers and nonsmokers.
Exposure–dose relationships for the lung
• Differing patterns of physical activity and ventilation for smokers and nonsmokers
• Differing patterns of lung deposition and clearance in smokers and nonsmokers
• Differing morphometry of target cells in smokers and nonsmokers
Carcinogenesis
• Other carcinogens and tobacco smoke carcinogens act at the same or different steps in a multistage carcinogenic process.
• Smokers and non-smokers differ on other, unmeasured modifying factors.

Table 2.3.2. Characteristics of case–control studies on the combined effect of asbestos exposure and smoking in the causation of lung cancer

Reference[a]	Location	Years of study	Study type and population	Controls	No. of cases[b]	Source of diagnosis
Martischnig *et al.* (1977)	Gateshead, UK	1972–73	Hospital-based; shipbuilding area	Patients	201	Confirmed clinical
Blot *et al.* (1978, 1980, 1982)	Georgia, Virginia, Florida, USA	1970–78	Shipbuilding areas	Patients and decedents, no chronic obstructive pulmonary disease	1072	Death certificates, medical records
Rubino *et al.* (1979)	Balangero, Italy	1946–75	Nested case–control study in chrysotile miners and millers	Alive when case died	12	Death certificates, medical records
Pastorino *et al.* (1984)	Lombardy, Italy	1976–79	Industrial areas	Population	204	Confirmed clinical
Kjuus *et al.* (1986)	Telemark and Vestfold, Norway	1979–83	Hospital-based; industrial and shipbuilding areas	Patients, no chronic obstructive pulmonary disease, other diseases precluding employment in heavy industry	176	Medical records
Garshick *et al.* (1987)	USA	1981–82	Railroad workers	Decedent, no cancer, accident, suicide, unknown cause	1081	Death certificates
De Klerk *et al.* (1991)	Wittenoom, Australia	1979–86	Nested case–control study in crocidolite miners and millers	Alive, no asbestos-related disease	40	Death certificates, medical records
Minowa *et al.* (1991)	Yokosuka, Japan	1979–82	Shipbuilding area	Decedent, no cancer, pneumoconiosis, accident, suicide	96	Confirmed clinical or autopsy
Bovenzi *et al.* (1993)	Trieste, Italy	1979–81, 1985–86	Industrial and shipbuilding area	Decedent, no chronic obstructive pulmonary disease, smoking-related cancer	516	Autopsy records
Gustavsson *et al.* (2002)	Stockholm, Sweden	1985–90	All men aged 40–75 years, residents of Stockholm County	1. Alive 2. Decedent, no tobacco-related disease	1038	Regional cancer register

Adapted from Lee (2001)

[a] Reference from which main results were obtained

[b] Number of cases with data on smoking and asbestos exposure

Table 2.3.3. Characteristics of cohort studies on the combined effect of asbestos exposure and smoking in the causation of lung cancer

Reference[a]	Location	Follow-up period	Study population	No. of cases[b]	Source of diagnosis
Elmes & Simpson (1971)	Belfast, Northern Ireland	1940–66	Insulation workers	19	Death certificates, medical records
Selikoff & Hammond (1975)	New York and New Jersey, USA	1943–74	Insulation workers	47	Death certificates, medical records
Hammond *et al.* (1979)	USA and Canada	1967–76	Insulation workers	276	Death certificates, medical records
Selikoff *et al.* (1980)	New Jersey, USA	1961–77	Amosite asbestos factory workers	50	Death certificates, medical records
Acheson *et al.* (1984)	Uxbridge, UK	1947–79	Amosite asbestos factory workers	22	Death certificates
Berry *et al.* (1985)	East London, UK	1960–70, 1971–80	Asbestos factory workers	79	Death certificates
Hilt *et al.* (1985)	Telemark, Norway	1953–80	Workers in nitric acid production plant	127	Death certificates
Neuberger & Kundi (1990)	Vöcklabruck, Austria	1950–87	Asbestos cement products workers	49	Death certificates, medical records
Hughes & Weill (1991)	New Orleans, USA	1969–83	Asbestos cement products workers	26	Death certificates
Cheng & Kong (1992)	Tianjin, China	1972–87	Chrysotile asbestos products workers	21	Not given (death)
McDonald *et al.* (1993)	Quebec, Canada	1950–92	Chrysotile miners and millers	299	Death certificates
Zhu & Wang (1993)	8 factories, China	1972–86	Chrysotile asbestos products workers	57	Death certificates, medical records
Meurman *et al.* (1994)	North Savo, Finland	1953–91	Anthophyllite miners	55	Cancer registration
Oksa *et al.* (1997)	Finland	1967–94	(1) Asbestos sprayers (2) Asbestosis patients (3) Silicosis patients	3 33 15	Cancer registry

Adapted from Lee (2001)

[a] Reference from which main results were obtained.

[b] Number of cases with data on smoking and exposure to asbestos

Table 2.3.4. Case–control studies on the combined effect of exposure to asbestos and smoking in the causation of lung cancer

Reference	Definition and source of asbestos exposure	Definition of smoking exposure	Relative risk[a]				Inter-action[b]
			Not exposed to asbestos or smoking	Exposed to asbestos but not smoking	Exposed to smoking but not asbestos	Exposed to smoking and asbestos	
Martischnig *et al.* (1977)	Yes *vs* no: questionnaire on work history	≥ 15 *vs* 0–14 cigarettes/day	1	1.08	1.78	5.57	> M
Blot *et al.* (1978, 1980, 1982)	Ever *vs* never worked in shipbuilding: interview of patients or proxies about work history	Current or former < 10 years					
		Georgia (n = 458)	1	1.28	4.71	7.58	~ M
		Virginia (n = 319)	1	1.88	3.09	4.87	~ M
		Florida (n = 295)	1	1.80	6.01	7.79	
Rubino *et al.* (1979)	≥ 101 *vs* 100 fibre–years: work history, dust measurements	Smoker *vs* nonsmoker	0	0	1	2.32	
Pastorino *et al.* (1984)	Yes *vs* no: interview of patients or proxies about work history	≥ 10 *vs* 0–9 cigarettes/day	1	2.82	5.47	9.86	I
Kjuus *et al.* (1986)	Heavy or moderate *vs* uncertain or none: interview of patients about asbestos exposure	≥ 10 *vs* 0–9 cigarettes/day	1	2.41	5.41	19.86	~ M
Garshick *et al.* (1987)	Yes *vs* no: work history	> 50 pack–years vs never smoker[c]					
		age < 65 years	1	1.20	5.68	6.82	
		age ≥ 65 years	1	0.98	9.14	8.96	
De Klerk *et al.* (1991)	High *vs* low: work history, dust measurements	Current or former < 10 years *vs* nonsmoker or former ≥ 10 years	1	2.24	3.44	9.57	> M
Minowa *et al.* (1991)	Definite or suspected *vs* none: interview of proxies about work history	Current or former < 10 years *vs* never-smoker or former > 10 years	1	–[d]	3.38	8.28	

Table 2.3.4 (contd)

Reference	Definition and source of asbestos exposure	Definition of smoking exposure	Relative risk[a]				Inter-action[b]
			Not exposed to asbestos or smoking	Exposed to asbestos but not smoking	Exposed to smoking but not asbestos	Exposed to smoking and asbestos	
Bovenzi *et al.* (1993)	Definite or possible *vs* none: interview of proxies about work history	Ever- *vs* never-smoker	1	1.83	10.13	15.89	
Gustavsson *et al.* (2002)	≥ 2.5 fibre–years *vs* none: reported work histories evaluated by an industrial hygienist and linked to workplace measurements	Current smoker *vs* never-smoker	1	10.2	21.7	43.1	

Adapted from Saracci & Boffetta (1994); Lee (2001)

[a] 0 indicates no cases in this category; 1 indicates reference group.

[b] Interaction term taken from Saracci & Boffetta (1994); numbers in parentheses are based on the assumption of a relative risk due to smoking of 10; A, additive; I, intermediate; M, multiplicative

[c] Fitted logistic regression assuming multiplicative model

[d] Not applicable because of zero division in odds ratio calculation

Table 2.3.5. Cohort studies on the combined effects of asbestos exposure and smoking in the causation of lung cancer

Reference	Definition and source of asbestos exposure	Definition of smoking exposure	Reference group[a]	Relative risk				Inter-action[c]
				Not exposed to asbestos or smoking	Exposed to asbestos but not smoking	Exposed to smoking but not asbestos[b]	Exposed to smoking and asbestos	
Elmes & Simpson (1971)	Study group: inferred from nature of population studied	Smoker *vs* nonsmoker	External	1	0[d]	(7.13)	112.94	
Selikoff & Hammond (1975)	Study group: inferred from nature of population studied	Ever *vs* never-smoker	External	1	8.44	(7.13)	73.71	(> M)
Hammond *et al.* (1979)	Study group: inferred from nature of population studied	Ever *vs* never-smoker	External	1	5.17	10.85	53.24	M
Selikoff *et al.* (1980)	Study group: inferred from nature of population studied	Ever *vs* never-smoker	External	1	25.00	(7.13)	33.44	I
Acheson *et al.* (1984)	Medium or heavy *vs* background: work history and dust measurements	Ever *vs* never-smoker	Internal External	0 1	1 6.07	0 (7.13)	2.57 15.53	(~ M)
Berry *et al.* (1985)	Severe *vs* low to moderate: work history	Ever *vs* never-smoker						
		(1960–70)	Internal					
		Men		1	0	1.15	1.93	(> M)
		Women		0	1	0	2.26	(> M)
		(1971–80)	External					
		Men		1	0	(7.13)	19.33	(A)
		Women		1	15.00	(7.13)	33.97	(I)
Hilt *et al.* (1985)	Exposed *vs* population controls: work history	Ever *vs* never-smoker	Internal	1	0	5.84	25.20	> M
Neuberger & Kundi (1990)	All workers: work history and dust measurements	Cigarettes/day smoked					[e]	
Hughes & Weill (1991)	Study group: work history and dust measurements	Ever *vs* never-smoker	External	1	0	(7.13)	~ 13	

Table 2.3.5 (contd)

Reference	Definition and source of asbestos exposure	Definition of smoking exposure	Reference group[a]	Relative risk				Inter-action[c]
				Not exposed to asbestos or smoking	Exposed to asbestos but not smoking	Exposed to smoking but not asbestos[b]	Exposed to smoking and asbestos	
Cheng & Kong (1992)	Yes *vs* no: work history and dust measurements	Cigarette smoker *vs* nonsmoker	Internal	1	5.44	1.57	8.73	M
McDonald *et al.* (1993)	≥ 60 *vs* < 60 million particles per cubic foot × years: work history and dust measurements	Ever *vs* never-smoker	Internal External	1 1	1.65 4.07	4.46 (7.13)	4.51 11.13	
Zhu & Wang (1993)	Yes *vs* no: work history and dust measurements	Smoker *vs* nonsmoker	Internal	1	3.78	1.83	11.06	
Meurman *et al.* (1994)	Heavy *vs* moderate: work history	Cigarette smoker *vs* nonsmoker	Internal External	1 1	0.83 3.21	6.27 (7.13)	6.16 23.87	
Oksa *et al.* (1997)	Study group: medical interview	Ever-smoker *vs* never-smoker	External					
		Asbestos sprayers		1	0	(7.13)	74.77	
		Patients with asbestosis		1	0	(7.13)	81.72	
		Patients with silicosis		1	0	(7.13)	22.34	

Adapted from Saracci & Boffetta (1994); Lee (2001)

[a] Internal: internal data for all four comparison groups; external: external reference group for asbestos-exposed groups

[b] The value of 7.13, shown in parentheses, is a value assumed by Lee (2001) and taken from the British Doctors' Study (see Section 2.0).

[c] Interaction term taken from Saracci & Boffetta (1994); numbers in parentheses are based on the assumption of a relative risk due to smoking of 10; A, additive; I, intermediate; M, multiplicative

[d] Only five nonsmokers at risk

[e] Graph showing that the observed number of deaths was close to that expected according to the workers' smoking habits, indicating that 'exposure to chrysotile does not increase lung cancer'

Table 2.3.6. Cohort studies on the combined effect of smoking and exposure to radon progeny in the causation of lung cancer

Reference[a]	Place of study	Years of study	Study population	Total cases/ cohort	Cases/cohort included	*p* value		Mixture	
						Multiplicative	Additive	λ	*p* value[b]
Radford & St Clair Renard (1984)	Sweden	1951–91	Iron miners	79/1294	51/1415	0.43	0.31	–0.3	0.38
Hornung & Meinhardt (1987)	Colorado, USA	1950–87	Uranium miners	329/3347	292/2205	0.58	0.04	0.7	0.49
Morrison *et al.* (1988)	Newfoundland, Canada	1950–84	Fluorspar miners	118/2088	25/1002	0.53	0.67	–0.1	0.85
Samet *et al.* (1991)	New Mexico, USA	1943–85	Uranium miners	69/3469	52/2602	0.15	0.11	0.4	0.16
Xuan *et al.* (1993)	Yunnan, China	1976–87	Tin miners	980/17 143	907/13 047	0.02	0.08	–0.3	0.39

Adapted from Lubin *et al.* (1994); NRC (1988)
[a] Most recent reference in 1994
[b]Refers to fit of mixture model versus full model.

Table 2.3.7. Case–control studies on the combined effect of smoking and radon exposure at home in the causation of lung cancer

Reference	Study location Years of study	No. of cases: Never-smoker/total	Findings
Axelson *et al.* (1988)	Sweden 1960–81	15/177	Increased risk for non- and occasional smokers vs. regular smokers in rural areas
Svensson *et al.* (1989)	Sweden 1983–85	35/210	Greater risk for smokers than never-smokers
Blot *et al.* (1990)	China 1985–87	123/308	Nonsignificantly greater risk in smokers ($p = 0.15$)
Schoenberg *et al.* (1990)	USA 1982–83	61/433	Exposure response strongest in light smokers; inverse in heaviest smokers
Ruosteenoja (1991)	Finland 1980–85	4/238	No pattern observed when heavier smokers compared with light smokers
Pershagen *et al.* (1994)	Sweden 1980–84	178/1360	Higher excess relative risk in current smokers than in never-smokers. Additivity rejected by data ($p = 0.02$)
Darby *et al.* (1998)	UK 1988–93	26/982	No evidence for heterogeneity of excess relative risk
Pisa *et al.* (2001)	Italy 1987–93	14/138	Interaction described as multiplicative, but analyses of interaction not significant
Wang *et al.* (2002)	China 1994–98	765/2009	No evidence for heterogeneity of excess relative risk

Adapted from NRC (1988)

Table 2.3.8. Studies on the combined effects of smoking and occupational exposure to arsenic on lung cancer

Reference Country and years of study	Study design	Source population	Exposure assessment (tobacco or arsenic)	No. of cases/ deaths	Smoking categories	Relative risks			Interaction/ excess risk (%)[a]	Comments
						Exposure categories				
Rencher *et al.* (1977) USA 1959–69	Proportional mortality cohort	522 workers at Utah copper smelter who died in 1959–69	Smoking history obtained from work supervisors of deceased employees	31 deaths		*Mine*	*Concentrator*	*Smelter*	69	
					Nonsmoker	1.0	1.1	4.7		
					Smoker	4.7	4.7	13.1		
Pershagen *et al.* (1981) Sweden 1928–77	Nested case–control	Cohort of 3958 workers at Ronnskar smelter employed for at least 3 months		76 deaths, 152 deceased controls		*No*	*Yes*		M; 131	Overlap of 41 cases with Pershagen (1985) and all 76 cases with Järup & Pershagen (1991)
					Nonsmoker	1.0	3.0			
					Smoker	4.9	14.6			
Welch *et al.* (1982) USA 1938–77	Cohort	1800 workers from Anaconda, MT, smelter: heavy exposure and a 20% random sample of other exposure categories	Arsenic categories based on quantified exposure estimates for one point in time	80 deaths		*Low*	*Medium*		M	Multiplicative interaction for (high + very high) vs low exposure
					Nonsmoker	1.0	0.9			
					Smoker	1.3	3.3			
						High	*Very high*			
					Nonsmoker	3.0	6.6			
					Smoker	3.8	8.5			
Pinto *et al.* (1978); Enterline (1983) USA 1949–73	Cohort	527 workers from Tacoma,WA, smelter who lived beyond age 65 and retired in 1949–73		32 deaths		*No*	*Yes*		(I); 91	
					Nonsmoker	1.0	5.1			
					Smoker	7.2	20.7			

Table 2.3.8 (contd)

Reference Country and years of study	Study design	Source population	Exposure assessment (tobacco or arsenic)	No. of cases/ deaths	Smoking categories	Relative risks Exposure categories			Interaction/ excess risk (%)[a]	Comments
Pershagen (1985) Sweden 1961–79	Case–control	Residents in region where the Ronnskar smelter is located		212 deaths, 424 deceased controls		*None*	*Residential*		Residential: 92 Mining: 105 Smelting: 71	Overlap of 52 cases with Järup & Pershagen (1991)
					Nonsmoker	1.0	2.3			
					Smoker	8.3	17.5			
						Mining	*Smelting*			
					Nonsmoker	10.4	8.4			
					Smoker	35.2	26.2			
Enterline *et al.* (1987) USA 1949–80	Nested case–control	Cohort of 2288[b] workers employed at 6 copper smelters for ≥ 3 years in 1946–76, terminating employment at age > 44 and after 1949	Arsenic exposure very low compared with other smelters	55 cases, 126 controls		*None*	*Mean exposure*		64	Included cases from study by Rencher *et al.* (1977). Fitted logistic model; mean exposure level over the six plants calculated as cumulative time-weighted average of 281.03 µg/m^3-years.
					Nonsmoker	1.0	2.1			
					Smoker for 20 years	2.4	5.1			
Taylor *et al.* (1989) China 1971–84	Retrospective nested case–control	Past and present workers at Yunnan Tin Corporation	Arsenic categories based on quantified exposure estimates	107 cases, 107 controls		*Low*	*Medium*	*High*	~ A	Cases alive in 1985 Tobacco smoked in a water pipe; very few nonsmokers; interaction calculated for heavy *vs* light smokers and high *vs* low exposure
					Light	1.0	3.2	5.0		
					Medium	1.0	4.9	4.4		
					Heavy	1.4	8.9	4.9		
Tsuda *et al.* (1990) Japan 1972–89	Cohort	141 certified arsenic poisoning patients	Employment in arsenic mines	8 deaths		*No*	*Yes*		(> M)	Standardized mortality ratio using sex- and age-specific mortality rate of all Japanese in 1975, 1980 or 1985
					SMR		264			
					Nonsmoker	0	1247			
					Smoker	0				
Järup & Pershagen (1991) Sweden 1928–81	Nested case–control	Cohort of 3916 workers at Ronnskar smelter employed at least 3 months from 1928–67	Smokers of > 10 g tobacco/ day; cumulative arsenic exposure	107 cases, 214 deceased controls excluding smoking-related causes		*Low*	*Medium*	*High*	Low: A Medium: ~ A High: I; 127	
					Nonsmoker	1.0	1.4	5.6		
					Smoker	40.1	9.4	29.2		

Adapted from Hertz-Picciotto *et al.* (1992); Saracci & Boffetta (1994)

[a] Terms for interaction were taken from Saracci and Boffetta (1994); terms in parentheses are based on the assumption that the relative risk is 10. A, additive; I, intermediate; M, multiplicative; the numbers are the percentage by which observed exceeds predicted excess relative risk and are taken from Hertz-Picciotto *et al.* (1992).

[b] Original paper reported 5392 workers in the six plants considered.

Table 2.3.9. Studies with information on interaction of smoking and alcohol in the causation of cancer at various sites

Reference	Place, year	Study population	Definition of tobacco/alcohol exposure	Alcohol categories	Smoking categories	Relative risk (95% CI)	Comments
Oral cavity							
Choi & Kahyo (1991)	Seoul, Republic of Korea, 1986–89	Cases: 113 men, 44 women (oral cavity) Controls: 339 men, 132 women; hospital controls, matched on age, sex and admission date	Alcohol (soju) in mL/day: Light: < 8100 Medium: 8100–16 200 Heavy: > 16 200	Non-drinker	Nonsmoker ≤ 1 pack/day > 1 pack/day	1.0 0.5 1	Stratified analysis; ORs extrapolated from figure [no formal test for interaction]
				Light drinker	Nonsmoker ≤ 1 pack/day > 1 pack/day	0.1 0.5 1.1	
				Medium drinker	Nonsmoker ≤ 1 pack/day > 1 pack/day	1.5 1.5 1.8	
				Heavy drinker	Nonsmoker ≤ 1 pack/day > 1 pack/day	1 2 5.04	
Zheng *et al.* (1997)	Beijing, China, 1988–89	Cases: 111 cases (tongue) Controls: 111 hospital controls, matched by age and sex	Alcohol: lifetime consumption	Never-drinker	Nonsmoker ≤ 20 pack–years > 20 pack–years	1.0 1.2 7.6*	Logistic regression model; risk estimates adjusted for education level. *$p < 0.05$ [No formal test for interaction]
				≤ 255 kg	Nonsmoker ≤ 20 pack–years > 20 pack–years	1.9 1.6 23.3*	
				> 255 kg	Nonsmoker ≤ 20 pack–years > 20 pack–years	2.4 3.0 4.1	
Schlecht *et al.* (1999)	Brazil, 1986–89	Cases: 373 incident cases (oral cavity) Controls: 746 hospital controls, matched on hospital, trimester of admission, age and sex	Alcohol: lifetime consumption	0–10 kg	0–5 pack–years 6–42 pack–years > 42 pack–years	1.0 2.9 (1.2–6.8) 7.8 (2.9–21.0)	Logistic regression model that included an interaction term; risk estimates adjusted for race, beverage temperature, religion, wood stove use and consumption of spicy foods; no statistical evidence for effect modification [*p* not stated]
				11–530 kg	0–5 pack–years 6–42 pack–years > 42 pack–years	1.2 (0.4–3.4) 6.2 (2.7–14.1) 11.2 (4.8–26.3)	
				> 530 kg	0–5 pack–years 6–42 pack–years > 42 pack–years	2.3 (0.6–9.1) 19.5 (2.6–147) 20.3 (9.0–45.3)	
Pharynx							
Olsen *et al.* (1985)	Denmark, 1980–82	Cases: 32 incident cases (hypopharynx) Controls: 1141 population controls, matched on sex, residence and age	Tobacco: g of tobacco/week	< 150 g/week	< 10 g/week ≥ 10 g/week	1.0 3.0 (1.3–6.9)	Stratified analysis [no formal test for interaction]
				≥ 150 g/week	< 10 g/week ≥ 10 g/week	1.7 (0.5–5.9) 5.2 (2.0–13.6)	

Table 2.3.9 (contd)

Reference	Place, year	Study population	Definition of tobacco/alcohol exposure	Alcohol categories	Smoking categories	Relative risk (95% CI)	Comments
Choi & Kahyo (1991)	Seoul, Republic of Korea, 1986–89	Cases: 133 men, 19 women (pharynx) Controls: 399 men, 57 women; hospital controls, matched on age, sex and admission date	Alcohol (soju) in mL/day: Light: < 8100 Medium: 8100–16 200 Heavy: > 16 200	Nondrinker	Nonsmoker ≤ 1 pack/day > 1 pack/day	1.0 0.8 1.0	Stratified analysis; ORs extrapolated from figure [no formal test for interaction]
				Light drinker	Nonsmoker ≤ 1 pack/day > 1 pack/day	1.1 0.9 1.3	
				Medium drinker	Nonsmoker ≤ 1 pack/day > 1 pack/day	1.0 1.5 1.2	
				Heavy drinker	Nonsmoker ≤ 1 pack/day > 1 pack/day	1.0 2.0 6.7	
Schlecht *et al.* (1999)	Brazil, 1986–89	Cases: 217 incident cases (pharynx) Controls: 434 hospital controls, matched on hospital, trimester of admission, age and sex	Alcohol: lifetime consumption	0–10 kg	0–5 pack–years 6–42 pack–years > 42 pack–years	1.0 2.4 (0.2–24.0) 69.4 (6.9–694)	Logistic regression model that included an interaction term; risk estimates were adjusted for race, beverage temperature, religion, wood stove use and consumption of spicy foods; interaction term statistically significant ($p = 0.007$)
				11–530 kg	0–5 pack–years 6–42 pack–years > 42 pack–years	6.2 (0.7–56.6) 21.7 (2.6–180) 43.0 (4.9–340)	
				> 530 kg	0–5 pack–years 6–42 pack–years > 42 pack–years	22.3 (2.1–238) 66.3 (1.7–2556) 77.3 (9.2–625)	

Table 2.3.9 (contd)

Reference	Place, year	Study population	Definition of tobacco/alcohol exposure	Alcohol categories	Smoking categories	Relative risk (95% CI)	Comments
Oesophagus							
Case–control studies							
Franceschi *et al.* (1990)	Northern Italy, 1986–89	Cases: 288 men, < 75 years old Controls: men < 75 years old, admitted to same hospitals for acute illness	*Tobacco*: Light: ex-smoker who quit ≥ 10 years ago or smoker of 1–14 cigs/day for < 30 years Moderate: 30–39 years duration regardless of amount, 15–24 cigs/day regardless of duration, 1–24 cigs/day for ≥ 40 yrs, or ≥ 15 cigs/day for < 30 yrs Heavy: ≥ 25 cigs/day for > 40 yrs *Alcohol*: 1 drink = 150 mL wine = 330 mL beer = 30 mL spirits	< 35 drinks/week 35–59 drinks/week ≥ 60 drinks/week 	Nonsmoker Light smoker Moderate smoker Heavy smoker Nonsmoker Light smoker Moderate smoker Heavy smoker Nonsmoker Light smoker Moderate smoker Heavy smoker	1.0 1.1 2.7 6.4 0.8 7.9 8.8 11.0 7.9 9.4 16.7 17.5	Regression model; risk estimates adjusted for age, area of residence and years of education [no formal test for interaction]
Barón *et al.* (1993)	Italy, 1989–91	Cases: 271 men Controls: 1754 men, hospital controls, matched on age and area of residence	Tobacco: Light: ex-smoker who quit ≥ 10 years ago or smokers of 1–14 cigs/day for < 30 years Moderate: 15–24 cigs/day regardless of duration or 30–39 years duration regardless of amount, or ≥ 15 cigs/day for < 30 years Heavy: ≥ 25 cigs/day for ≥ 40 years	< 35 drinks/week 35–59 drinks/week ≥ 60 drinks/week 	Nonsmoker Light smoker Moderate smoker Heavy smoker Nonsmoker Light smoker Moderate smoker Heavy smoker Nonsmoker Light smoker Moderate smoker Heavy smoker	1.0 2.1 4.4 8.4 2.2 4.4 9.7 18.5 2.6 5.5 11.4 21.8	Regression model; risk estimates adjusted for area of residence, age, education and profession [no formal test for interaction]

Table 2.3.9 (contd)

Reference	Place, year	Study population	Definition of tobacco/alcohol exposure	Alcohol categories	Smoking categories	Relative risk (95% CI)	Comments
Brown *et al.* (1994a)	Georgia, Michigan, New Jersey, USA, 1986–89	Cases: 373 men (squamous-cell carcinoma) (124 white, 249 black) Controls: 1364 men, community controls (750 white, 614 black)	Tobacco: Light: nonsmoker, former smoker or current smoker of < 1 pack/day Heavy: current smoker of ≥ 1 pack/day	White men 0–7 drinks/week 8–14 drinks/week 15–35 drinks/week 36–84 drinks/week ≥ 85 drinks/week Black men 0–7 drinks/week 8–14 drinks/week 15–35 drinks/week 36–84 drinks/week ≥ 85 drinks/week	 Light smoker Heavy smoker Light smoker Heavy smoker Light smoker Heavy smoker Light smoker Heavy smoker Light smoker Heavy smoker Light smoker Heavy smoker Light smoker Heavy smoker Light smoker Heavy smoker Light smoker Heavy smoker Light smoker Heavy smoker	 1.0 3.3 (1.0–19.8) 1.8 (0.5–6.1) 8.7 (2.4–32.4) 4.6 (1.7–12.8) 22.1 (7.8–62.3) 19.7 (7.2–53.4) 28.5 (10.1–80.2) 29.0 (7.2–116.5) 35.4 (10.0–125.5) 1.0 4.5 (1.4–14.6) 5.7 (2.0–15.8) 14.2 (4.1–49.1) 10.6 (4.1–27.2) 36.8 (13.9–97.2) 39.5 (14.5–107.8) 42.1 (15.8–112.6) 31.0 (9.8–98.5) 149.2 (39.2–567.4)	Logistic regression model; risk estimates adjusted for age, geographical area and income. For both races, interaction between smoking and drinking was not significant [p value not provided]. Significant interaction ($p = 0.02$) between race and smoking/drinking variable
Brown *et al.* (1994b)	Georgia, Michigan, New Jersey, USA, 1986–89	Cases: 174 white men (adenocarcinoma) Controls: 750 men, community controls, frequency-matched on age and race		< 8 drinks/week ≥ 8 drinks/week	< 1 pack/day ≥ 1 pack/day < 1 pack/day ≥ 1 pack/day	1.0 2.4 (1.5–3.8) 2.4 (1.1–5.1) 3.8 (2.2–6.4)	Unconditional logistic regression model; risk estimates adjusted for age, area, and income; not possible to distinguish statistically between additive, multiplicative and intermediate models. [No formal test for interaction]

Table 2.3.9 (contd)

Reference	Place, year	Study population	Definition of tobacco/alcohol exposure	Alcohol categories	Smoking categories	Relative risk (95% CI)	Comments
Castelletto *et al.* (1994)	La Plata, Argentina, 1986–89	Cases: 131 incident cases Controls: 262 hospital controls, matched for age and hospital		0 mL/day	Nonsmoker	1.0	Logistic regression model; risk estimates adjusted for age, sex, hospital and education. Test for interaction between alcohol and tobacco not significant ($p = 0.45$)
					1–14 cigs/day	2.5 (0.4–16.5)	
					≥ 15 cigs/day	0.7 (0.1–6.5)	
				1–99 mL/day	Nonsmoker	1.6 (0.6–4.2)	
					1–14 cigs/day	4.3 (1.4–13.2)	
					≥ 15 cigs/day	3.7 (1.3–11.0)	
				100–199 mL/day	Nonsmoker	1.2 (0.1–12.0)	
					1–14 cigs/day	3.7 (1.3–11.0)	
					≥ 15 cigs/day	11.8 (3.7–37.7)	
				≥ 200 mL/day	Nonsmoker	5.7 (1.1–28.6)	
					1–14 cigs/day	5.0 (0.6–39.1)	
					≥ 15 cigs/day	19.0 (5.4–66.9)	
Hu *et al.* (1994)	Heilongjiang Province, China, 1985–1989	Cases: 196 incident cases Controls: 392 hospital controls (non-neoplastic, non-oesophageal disease), matched on age, gender and area of residence		≤ 57 L liquor/year	Nonsmoker	1.0	Regression model that does not assume multiplicative effects; synergistic effect that accounts for 38% of the excess risk [no formal test for interaction]: when using data in continuous form, interaction terms in the regression models were not significant.
					1–30 cigs/day	1.8	
					≥ 31 cigs/day	4.5	
				> 57 L liquor/year	Nonsmoker	1.0	
					1–30 cigs/day	5.3	
					≥ 31 cigs/day	7.9	
Zambon *et al.* (2000)	Northern Italy, 1992–97	Cases: 275 men (incident squamous-cell carcinoma) Controls: 593 men, hospital controls	Alcohol: 1 drink = 125 mL wine = 330 mL beer = 30 mL spirits	0–20 drinks/week	Nonsmoker	1.0	Logistic regression model; risk estimates adjusted for area of residence, age and education; risk increase for the highest joint level of alcohol drinking and current smoking compatible with a multiplicative model (departure from multiplicativity $\beta = 0.15$, $p = 0.27$)
					1–14 cigs/day	–	
					15–24 cigs/day	3.3 (0.4–31.1)	
					≥ 25 cigs/day	–	
				21–34 drinks/week	Nonsmoker	2.1 (0.2–23.5)	
					1–14 cigs/day	18.9 (2.2–161.8)	
					15–24 cigs/day	35.3 (4.3–288.9)	
					≥ 25 cigs/day	44.1 (5.5–352.9)	
				35–59 drinks/week	Nonsmoker	8.9 (1.0–77.8)	
					1–14 cigs/day	36.5 (4.4–305.7)	
					15–24 cigs/day	57.2 (7.2–456.9)	
					≥ 25 cigs/day	66.8 (7.8–573.3)	
				≥ 60 drinks/week	Nonsmoker	56.1 (6.2–508.0)	
					1–14 cigs/day	40.3 (4.6–355.4)	
					15–24 cigs/day	117.6 (15.0–923.1)	
					≥ 25 cigs/day	130.3 (15.2–980.1)	

Table 2.3.9 (contd)

Reference	Place, year	Study population	Definition of tobacco/alcohol exposure	Alcohol categories	Smoking categories	Relative risk (95% CI)	Comments
Cohort study							
Kinjo *et al.* (1998)	Japan, 1966–81	Six-prefecture study (see Table 2.1) 440 deaths		≤ 3 times/week	Nonsmoker ≥ 1 cig/day	1.0 1.6 (1.1–2.1)	Risk estimates adjusted for attained age, prefecture, occupation and sex. Joint effect of alcohol drinking and smoking was more than additive. Data available for interaction of tobacco and alcohol stratified by tea consumption (hot/not hot)
				≥ 4 times/week	Nonsmoker ≥ 1 cig/day	1.0 (0.4–2.0) 3.9 (2.7–5.4)	
Larynx							
Wynder *et al.* (1976)	New York City, Houston, Los Angeles, Birmingham, Miami, New Orleans, USA, 1970–73	Cases: 258 men, 56 women Controls: 516 men, 168 women; hospital controls, matched on gender, year of interview, hospital status and age at diagnosis	*Tobacco*: 1 cigar = 5 cig. 1 pipe = 2.5 cig. *Alcohol*: 1 unit = 1 oz spirits = 4 oz wine = 6 oz beer	Men Nondrinker	Nonsmoker 1–15 cigs/day 16–34 cigs/day ≥ 35 cigs/day	1.0 3.0 (1.0–9.1) 6.0 (2.2–16.1) 7.0 (2.5–19.4)	Stratified analysis [no formal test for interaction]
				1–6 units/day	Nonsmoker 1–15 cigs/day 16–34 cigs/day ≥ 35 cigs/day	– 4.0 (1.0–15.6) 6.7 (2.3–19.7) 10.3 (3.6–29.8)	
				≥ 7 units/day	Nonsmoker 1–15 cigs/day 16–34 cigs/day ≥ 35 cigs/day	– 3.3 (0.9–12.8) 13.8 (5.1–37.7) 22.1 (7.8–62.1)	
Burch *et al.* (1981)	Ontario, Canada, 1977–79	Cases: 204 incident cases Controls: 204 community controls, matched on neighbourhood, sex and age	*Tobacco*: lifetime cigarette consumption *Alcohol*: lifetime oz ethanol consumption	0 oz	Nonsmoker < 150 000 cigs 150 000–299 000 cigs ≥ 300 000 cigs	1.0 2.0 3.9 7.6	Logistic regression model; coefficient for the interaction term (–0.10) not significant (SE = 0.11, $p = 0.177$)
				< 10 000 oz	Nonsmoker < 150 000 cigs 150 000–299 000 cigs ≥ 300 000 cigs	2.0 3.5 6.3 11.1	
				10 000–25 000 oz	Nonsmoker < 150 000 cigs 150 000–299 000 cigs ≥ 300 000 cigs	3.9 6.3 10.1 16.3	
				≥ 26 000 oz	Nonsmoker < 150 000 cigs 150 000–299 000 cigs ≥ 300 000 cigs	7.7 11.2 16.3 23.7	

Table 2.3.9 (contd)

Reference	Place, year	Study population	Definition of tobacco/alcohol exposure	Alcohol categories	Smoking categories	Relative risk (95% CI)	Comments
Flanders & Rothman (1982)	7 cities and 2 states in the USA, 1969–71	Cases: 87 men Controls: 956 men with cancers of other sites (excluding oral cavity, pharynx, oesophagus, stomach, lung, small intestine, colon, pancreas, bronchus, pleura, bladder and kidney)	Tobacco and alcohol: lifetime consumption in units 1 tobacco unit = 1 cigarette = 0.2 cigars = 0.4 pipefuls 1 alcohol unit = 1.5 oz spirits = 6 oz wine = 12 oz beer			Index of interaction[†]	[†]A value of 1.0 indicates no synergy.
				0–49 units	0–49 units	–	
					50–549 units	–	
					550–899 units	–	
					≥ 900 units	–	
				50–349 units	0–49 units	–	
					50–549 units	0.1	
					550–899 units	1.8	
					≥ 900 units	1.1	
				350–699 units	0–49 units	–	
					50–549 units	6.1	
					550–899 units	0.7	
					≥ 900 units	1.6	
				≥ 700 units	0–49 units	–	
					50–549 units	3.0	
					550–899 units	0.7	
					≥ 900 units	1.3	
			Daily consumption	0 units	0 unit	–	
					1–14 units	–	
					15–34 units	–	
					≥ 35 units	–	
				1–9 units	0 unit	–	
					1–14 units	2.3	
					15–34 units	1.2	
					≥ 35 units	1.7	
				≥ 9 units	0 unit	–	
					1–14 units	1.8	
					15–34 units	3.0	
					≥ 35 units	3.9	
Herity *et al.* (1982)	Dublin, Ireland	Cases: 59 men Controls: 152 men, hospital controls		Non-/light drinker	Non-/light smoker	1.0	Stratified analysis; synergistic effect between alcohol and tobacco, index of interaction = 2.5
					Heavy smoker	3.3 (1.2–9.1)	
				Heavy drinker	Non-/light smoker	4.0 (1.6–9.9)	
					Heavy smoker	14.0 (6.3–31.0)	

Table 2.3.9 (contd)

Reference	Place, year	Study population	Definition of tobacco/alcohol exposure	Alcohol categories	Smoking categories	Relative risk (95% CI)		Comments
						LL	FL	
Walter & Iwane (1983)	7 cities and 2 states in the USA, 1969–71	Cases: 87 men Controls: 956 men with cancers of other sites (excluding oral cavity, pharynx, oesophagus, stomach, lung, small intestine, colon, pancreas, bronchus, pleura, bladder and kidney	Tobacco and alcohol: lifetime consumption in units 1 tobacco unit = 1 cigarette = 0.2 cigars = 0.4 pipefuls 1 alcohol unit = 1.5 oz spirits = 6 oz wine = 12 oz beer	0–49 units	0–49 units	1.0	1.0	Reanalysis of the data from Flanders and Rothman (1982); risk estimates adjusted for age LL = log linear model; FL = Flanders and Rothman model
					50–549 units	1.7	1.5	
					550–899 units	2.6	3.5	
					≥ 900 units	5.4	7.9	
				50–349 units	0–49 units	1.5	1.1	
					50–549 units	2.5	1.9	
					550–899 units	3.8	4.7	
					≥ 900 units	7.9	11.1	
				350–699 units	0–49 units	2.0	2.5	
					50–549 units	3.3	4.0	
					550–899 units	5.1	6.8	
					≥ 900 units	10.5	13.3	
				≥ 700 units	0–49 units	3.0	6.1	
					50–549 units	5.0	9.3	
					550–899 units	7.9	12.1	
					≥ 900 units	16.2	18.5	
Brownson & Chang (1987)	Missouri, USA, 1972–84	Cases: 63 white men Controls: 200 white men with colon cancer	Smoking (yes/no) Drinking (yes/no)	No alcohol	No smoking	1.0		Logistic regression model; risk estimates adjusted for age. Synergy index used to measure interaction between smoking and alcohol = 1.77 (77% greater than predicted additivity).
					Smoking	3.4		
				Alcohol	No smoking	2.4		
					Smoking	7.7		
De Stefani *et al.* (1987)	Uruguay, 1985–86	Cases: 107 men, aged 30–89 years Controls: 290 men, hospital controls		0–64 mL/day	0–15 cigs/day	1.0		Stratified analysis [no formal test for interaction]
					≥ 16 cigs/day	20.6		
				≥ 65 mL/day	0–15 cigs/day	16.7		
					≥ 16 cigs/day	123.4		

Table 2.3.9 (contd)

Reference	Place, year	Study population	Definition of tobacco/alcohol exposure	Alcohol categories	Smoking categories	Relative risk (95% CI)	Comments
Guénel *et al.* (1988)	Curie Institute, Paris, 1975–85	Cases: 411 men, ≥ 25 years old Controls: 4135 men, community controls, ≥ 25 years old	Tobacco: g tobacco/day	*Glottis (n = 197)*			Stratified analysis; risk estimates adjusted for age. To test deviation from the multiplicative model, a logistic model with cross-product variables alcohol × tobacco was compared to the simple multiplicative model: Glottis: chi-squared =10.2, $p = 0.33$ (9 degrees of freedom); Supraglottis: chi-squared = 4.78, $p = 0.85$ (9 degrees of freedom) [This indicated that the multiplicative model fits well.]
				0–39 g/day	0–9 g/day	1.0	
					10–19 g/day	0.4 (0.2-4.5)	
					20–29 g/day	9.3 (4.9-36.4)	
					≥ 30 g /day	19.2 (7.7-58.4)	
				40–99 g/day	0–9 g/day	1.6 (0.6-4.1)	
					10–19 g/day	2.9 (1.1-8.0)	
					20–29 g/day	12.3 (4.3-27.5)	
					≥ 30 g /day	27.4 (8.4-64.4)	
				100–159 g/day	0–9 g/day	2.8 (1.2-15.2)	
					10–19 g/day	15.1 (5.2-43.4)	
					20–29 g/day	26.4 (7.8-62.3)	
					≥ 30 g /day	48.9 (16.9-132.8)	
				≥ 160 g/day	0–9 g/day	5.1 (2.3-53.8)	
					10–19 g/day	40.9 (10.3-191.5)	
					20–29 g/day	125.3 (34.1-367.4)	
					≥ 30 g /day	289.4 (83.0-705.8)	
				Supraglottis (n = 214)			
				0–39 g/day	0–9 g/day	1.0	
					10–19 g/day	3.4 (0.6–20.9)	
					20–29 g/day	32.3 (4.4–82.1)	
					≥ 30 g /day	46.8 (6.7–152.6)	
				40–99 g/day	0–9 g/day	2.6 (0.3–10.4)	
					10–19 g/day	27.5 (2.1–49.8)	
					20–29 g/day	48.5 (6.7–101.0)	
					≥ 30 g /day	132.3 (16.6–283.8)	
				100–159 g/day	0–9 g/day	7.3 (1.6–57.3)	
					10–19 g/day	75.4 (8.4–187.0)	
					20–29 g/day	180.7 (27.3–415.2)	
					≥ 30 g /day	530.6 (77.7–1175.7)	
				≥ 160 g/day	0–9 g/day	50.6 (8.4–280.2)	
					10–19 g/day	115.5 (22.8–671.0)	
					20–29 g/day	647.7 (106.4–1749.1)	
					≥ 30 g /day	1094.2 (185.8–2970.7)	

Table 2.3.9 (contd)

Reference	Place, year	Study population	Definition of tobacco/alcohol exposure	Alcohol categories	Smoking categories	Relative risk (95% CI)	Comments
Tuyns *et al.* (1988)	France, Italy, Spain, Switzerland	Cases: 1147 men Controls: 3057 men, population controls, individually matched on area and frequency-matched on age		*Endolarynx*			Logistic regression model
				0–40 g/day	0–7 cigs/day	1.0	
					8–15 cigs/day	6.7	
					16–25 cigs/day	12.7	
					≥ 26 cigs/day	11.5	
				41–80 g/day	0–7 cigs/day	1.7	
					8–15 cigs/day	5.9	
					16–25 cigs/day	12.2	
					≥ 26 cigs/day	18.5	
				81–120 g/day	0–7 cigs/day	2.3	
					8–15 cigs/day	10.7	
					16–25 cigs/day	21.0	
					≥ 26 cigs/day	23.6	
				≥ 121 g/day	0–7 cigs/day	3.8	
					8–15 cigs/day	12.2	
					16–25 cigs/day	31.6	
					≥ 26 cigs/day	43.2	For multiplicative model, chi-squared = 5.8 (9 degrees of freedom)
				Hypopharynx/epilarynx			
				0–40 g/day	0–7 cigs/day	1.0	
					8–15 cigs/day	4.7	
					16–25 cigs/day	13.9	
					≥ 26 cigs/day	4.9	
				41–80 g/day	0–7 cigs/day	3.0	
					8–15 cigs/day	14.6	
					16–25 cigs/day	19.5	
					≥ 26 cigs/day	18.4	
				81–120 g/day	0–7 cigs/day	5.5	
					8–15 cigs/day	27.5	
					16–25 cigs/day	48.3	
					≥ 26 cigs/day	37.6	
				≥ 121 g/day	0–7 cigs/day	14.7	
					8–15 cigs/day	71.6	
					16–25 cigs/day	67.8	
					≥ 26 cigs/day	135.5	For multiplicative model, chi-squared = 14.5 (9 degrees of freedom)

Table 2.3.9 (contd)

Reference	Place, year	Study population	Definition of tobacco/alcohol exposure	Alcohol categories	Smoking categories	Relative risk (95% CI)	Comments
Falk *et al.* (1989)	Texas, USA, 1975–80	Cases: 151 living white men, aged 30–79 years Controls: 235 living white men, community controls		< 4 drinks/week	Nonsmoker 1–10 cigs/day 11–20 cigs/day 21–39 cigs/day ≥ 40 cigs/day	1.0 2.9 (2.2–3.9) 5.2 (2.5–10.7) 8.0 (5.8–11.0) 10.2 (8.6–12.2)	Logistic regression model; risk estimates adjusted for age Goodness-of-fit for additive model: chi-squared = 4.44, $p = 0.73$ Goodness-of-fit for multiplicative model: chi-squared = 4.09, $p = 0.77$
				≥ 4 drinks/week	Nonsmoker 1–10 cigs/day 11–20 cigs/day 21–39 cigs/day ≥ 40 cigs/day	1.8 (1.5–2.1) 4.6 (3.1–6.7) 6.5 (3.5–12.0) 10.5 (7.8–14.2) 15.4 (10.9–21.9)	
Franceschi *et al.* (1990)	Northern Italy, 1986–89	Cases: 162 men < 75 years old Controls: Men < 75 years old admitted to same hospitals for acute illness	*Tobacco*: Light: ex-smoker who quit ≥ 10 years ago or smokers of 1–14 cigs/day for < 30 years Moderate: 30–39 years duration regardless of amount, 15–24 cigs/day regardless of duration, 1–24 cigs/day for ≥ 40 years, or ≥ 15 cigs/day for < 30 years Heavy: ≥ 25 cigs/day for > 40 years *Alcohol*: 1 drink = 150 mL wine = 330 mL beer = 30 mL spirits	< 35 drinks/week	Nonsmoker Light smoker Moderate smoker Heavy smoker	1.0 0.9 4.5 6.1	Regression model; risk estimates adjusted for age, area of residence and years of education. [No formal test for interaction]
				35–59 drinks/week	Nonsmoker Light smoker Moderate smoker Heavy smoker	1.6 5.0 7.1 10.4	
				≥ 60 drinks/week	Nonsmoker Light smoker Moderate smoker Heavy smoker	– 5.4 9.5 11.7	

Table 2.3.9 (contd)

Reference	Place, year	Study population	Definition of tobacco/alcohol exposure	Alcohol categories	Smoking categories	Relative risk (95% CI)	Comments
Choi & Kahyo (1991)	Seoul, Republic of Korea, 1986–89	Cases: 94 men, 6 women Controls: 282 men, 18 women; hospital controls, matched on age, sex and admission date	Alcohol (soju) in mL/day: Light: < 8100 Medium: 8100–16 200 Heavy: > 16 200	Non-drinker	Nonsmoker ≤ 1 pack/day > 1 pack/day	1.0 2 4	Stratified analysis; ORs extrapolated from figure [No formal test for interaction]
				Light drinker	Nonsmoker ≤ 1 pack/day > 1 pack/day	0.5 0.8 1.0	
				Medium drinker	Nonsmoker ≤ 1 pack/day > 1 pack/day	1.5 3 2.5	
				Heavy drinker	Nonsmoker ≤ 1 pack/day > 1 pack/day	0.5 4 20.7	
Freudenheim *et al.* (1992)	New York, USA, 1975–85	Cases: 250 incident (white) cases Controls: 250 (white) neighbourhood controls, matched on age	Alcohol: Drink–years = drinks/month multiplied by number of years of drinking	≤ 1243 drink–years	≤ 24 pack–years > 24 pack–years	1.0 2.7 (1.4–5.2)	Logistic regression model; risk estimates adjusted for education; interaction between tobacco and alcohol [no formal test for interaction]
				> 1243 drink–years	≤ 24 pack–years > 24 pack–years	0.98 (0.5–2.1) 5.8 (3.3–10.4)	
Zheng *et al.* (1992)	Shanghai, 1988–90	Cases: 201 incident cases Controls: 414 community controls, frequency-matched on sex and age	Alcohol lifetime consumption	Men			Stratified analysis; risk estimates adjusted for age and education [no formal test for interaction]
				Non-drinker	0–9 pack–years 10–29 pack–years ≥ 30 pack–years	1.0 3.1 (1.1–8.7) 35.7 (13.6–93.9)	
				< 300 kg	0–9 pack–years 10–29 pack–years ≥ 30 pack–years	1.0 (0.2–5.5) 3.8 (1.1–12.1) 12.1 (3.8–38.6)	
				300–899 kg	0–9 pack–years 10–29 pack–years ≥ 30 pack–years	7.5 (1.4–38.8) 3.7 (1.1–12.0) 23.2 (8.3–65.0)	
				≥ 900kg	0–9 pack–years 10–29 pack–years ≥ 30 pack–years	2.5 (0.2–27.0) 7.4 (1.0–55.0) 25.1 (9.6–70.0)	

Table 2.3.9 (contd)

Reference	Place, year	Study population	Definition of tobacco/alcohol exposure	Alcohol categories	Smoking categories	Relative risk (95% CI)	Comments
Barón *et al.* (1993)	Italy, 1989–91	Cases: 224 men Controls: 1754 men, hospital controls, matched on age and residence	Tobacco: Light: ex-smoker who quit ≥ 10 years ago or smokers of 1–14 cigs/day for < 30 years Moderate: 15–24 cigs/day regardless of duration or 30–39 years duration regardless of amount, or ≥ 15 cigs/day for < 30 years Heavy: ≥ 25 cigs/day for ≥ 40 years	< 35 drinks/week 35–59 drinks/week ≥ 60 drinks/week	Nonsmoker Light smoker Moderate smoker Heavy smoker Nonsmoker Light smoker Moderate smoker Heavy smoker Nonsmoker Light smoker Moderate smoker Heavy smoker	1.0 1.3 5.2 11.2 1.3 1.7 6.8 14.6 1.9 2.5 9.9 21.3	Regression model; risk estimates adjusted for area of residence, age, education and profession [no formal test for interaction]
Dosemeci *et al.* (1997)	Turkey, 1979–84	Cases: 832 men Controls: 829 men, hospital controls with selected cancers		Never-drinker 1–20 drink–years ≥ 21 drink–years	Nonsmoker 1–20 cigs/day ≥ 21 cigs/day Nonsmoker 1–20 cigs/day ≥ 21 cigs/day Nonsmoker 1–20 cigs/day ≥ 21 cigs/day	1.0 3.0 (2.2–4.1) 6.2 (3.9–9.9) – 5.6 (3.2–9.8) 6.0 (2.5–14.3) – 5.2 (1.9–15.1) 12.2 (3.1–57.6)	Stratified analysis; risk estimates also provided for glottis, supraglottis and other sites [no formal test for interaction]
Schlecht *et al.* (1999)	Brazil, 1986–89	Cases: 194 incident cases Controls: 388 hospital controls, matched on hospital, trimester of admission, age and sex	Alcohol: lifetime consumption	0–10 kg 11–530 kg > 530 kg	0–5 pack–years 6–42 pack–years > 42 pack–years 0–5 pack–years 6–42 pack–years > 42 pack–years 0–5 pack–years 6–42 pack–years > 42 pack–years	1.0 13.5 (2.7–66.8) 11.4 (2.1–62.0) 1.2 (0.1–14.4) 16.1 (3.4–76.2) 22.0 (4.5–107) 5.5 (0.4–71.5) 36.9 (0.7–1800) 43.1 (9.1–208)	Logistic regression model that included an interaction term; risk estimates adjusted for race, beverage temperature, religion, wood stove use and consumption of spicy foods. No statistical evidence for effect modification ($p = 0.945$)

Table 2.3.9 (contd)

Reference	Place, year	Study population	Definition of tobacco/alcohol exposure	Alcohol categories	Smoking categories	Relative risk (95% CI)	Comments
Mixed upper aerodigestive tract (ADT)							
Case–control studies							
Franceschi *et al.* (1990)	Northern Italy, 1986–89	Cases: 157 men < 75 years old Controls: 1272 men < 75 years old, admitted to same hospitals for acute illness	*Tobacco*: Light: ex-smoker who quit ≥ 10 years ago or smokers of 1–14 cigs/day for < 30 years Moderate: 30–39 years duration regardless of amount, 15–24 cigs/day regardless of duration, 1–24 cigs/day for ≥ 40 yrs, or ≥ 15 cigs/day for < 30 years Heavy: ≥ 25 cigs/day for > 40 yrs *Alcohol*: 1 drink = 150 mL wine = 330 mL beer = 30 mL spirits	< 35 drinks/week 35–59 drinks/week ≥ 60 drinks/week	Nonsmoker Light smoker Moderate smoker Heavy smoker Nonsmoker Light smoker Moderate smoker Heavy smoker Nonsmoker Light smoker Moderate smoker Heavy smoker	1.0 3.1 10.9 17.6 1.6 5.4 26.6 40.2 2.3 10.9 36.4 79.6	Logistic regression model; risk estimates adjusted for age, area of residence, education and occupation [no formal test for interaction]
Maier *et al.* (1992)	Germany, 1987–88	Cases: 200 men (squamous-cell cancer of the head and neck) Controls: 800 men, outpatient clinic controls	Tobacco: 1 tobacco–year = daily consumption of 20 cigarettes, 4 cigars, or 5 pipes for 1 year	< 25 g/day 25–75 g/day > 75 g/day	< 5 tobacco-years 5–50 tobacco-years > 50 tobacco-years < 5 tobacco-years 5–50 tobacco-years > 50 tobacco-years < 5 tobacco-years 5–50 tobacco-years > 50 tobacco-years	1.0 5.7 (1.9–17.3) 23.3 (6.6–82.5) 2.3 (0.6–8.8) 14.6 (4.8–43.9) 52.8 (15.8–176.6) 10.3 (1.9–55.8) 153.2 (44.1–532) 146.2 (37.7–566)	Logistic regression model; combined consumption of alcohol and tobacco increased the risk in a multiplicative manner. [No formal test for interaction]

Table 2.3.9 (contd)

Reference	Place, year	Study population	Definition of tobacco/alcohol exposure	Alcohol categories	Smoking categories	Relative risk (95% CI)	Comments
Barón *et al.* (1993)	Italy, 1989–91	Cases: 308 men (oral or pharyngeal cancer) Controls: 1754 men, hospital controls, matched on age and area of residence	Tobacco: Light: ex-smoker who quit ≥ 10 years ago or smokers of 1–14 cigs/day for < 30 years Moderate: 15–24 cigs/day regardless of duration or 30–39 years duration regardless of amount, or ≥ 15 cigs/day for < 30 years Heavy: ≥ 25 cigs/day for ≥ 40 years	< 35 drinks/week 35–59 drinks/week ≥ 60 drinks/week	Nonsmoker Light smoker Moderate smoker Heavy smoker Nonsmoker Light smoker Moderate smoker Heavy smoker Nonsmoker Light smoker Moderate smoker Heavy smoker	1.0 6.4 5.4 32.1 3.6 23.0 91.4 115.6 9.5 60.8 241.3 304.9	Regression model; risk estimates adjusted for area of residence, age, education and profession [no formal test for interaction]
Kune *et al.* (1993)	Melbourne, Australia, 1982	Cases: 41 men, incident cases (19 oral, 22 pharynx) Controls: 398 men, community controls		≤ 200 g/week > 200 g/week	Non/former smoker Current smoker Non/former smoker Current smoker	1.0 25.2 (3.1–204) 42.7 (5.5–330) 111.8 (15.5–865)	Logistic regression model; more than additive interaction [no formal test for interaction]

Table 2.3.9 (contd)

Reference	Place, year	Study population	Definition of tobacco/alcohol exposure	Alcohol categories	Smoking categories	Relative risk (95% CI)	Comments
Mashberg *et al.* (1993)	New Jersey, USA, 1972–83	Cases: 359 [men] (oral cavity-oropharynx) Controls: 2280 [men], hospital controls	Alcohol: 1 whisky equivalent (WE) = 10.24 g ethanol	0–1 WE/day	0–5 cigs/day	1.0	Logistic regression model; risk estimates adjusted for age; results suggest multiplicative interaction [no formal test for interaction] $*p < 0.05$
					6–15 cigs/day	10.8	
					16–25 cigs/day	7.6	
					26–35 cigs/day	–	
					≥ 36 cigs/day	3.2	
				2–5 WE/day	0–5 cigs/day	2.7	
					6–15 cigs/day	24.2*	
					16–25 cigs/day	29.7*	
					26–35 cigs/day	5.3	
					≥ 36 cigs/day	10.2*	
				6–10 WE/day	0–5 cigs/day	11.9	
					6–15 cigs/day	50.9*	
					16–25 cigs/day	28.9*	
					26–35 cigs/day	61.9*	
					≥ 36 cigs/day	26.8*	
				11–21 WE/day	0–5 cigs/day	12.5*	
					6–15 cigs/day	30.9*	
					16–25 cigs/day	44.8*	
					26–35 cigs/day	79.5*	
					≥ 36 cigs/day	98.4*	
				≥ 22 WE/day	0–5 cigs/day	8.3	
					6–15 cigs/day	27.5*	
					16–25 cigs/day	61.7*	
					26–35 cigs/day	70.3*	
					≥ 36 cigs/day	32.0*	

Table 2.3.9 (contd)

Reference	Place, year	Study population	Definition of tobacco/alcohol exposure	Alcohol categories	Smoking categories	Relative risk (95% CI)	Comments
Kabat *et al.* (1994)	8 cities in the USA, 1977–90	Cases: 1097 men, 463 women, incident cases (oral cavity, pharynx) Controls: 2075 men, 873 women; hospital controls		*Men*			Logistic regression model; risk estimates adjusted for age, years of schooling, race, time period and type of hospital
				Nondrinker	Nonsmoker	1.0	
					Former smoker	1.1 (0.7–1.6)	
					1–20 cigs/day	1.5 (0.9–2.5)	
					21–30 cigs/day	2.2 (1.1–4.3)	
					≥ 31 cigs/day	2.0 (1.1–3.7)	
				1–3.9 oz/day	Nonsmoker	1.6 (0.9–2.7)	
					Former smoker	1.7 (1.1–2.6)	
					1–20 cigs/day	5.8 (3.7–9.1)	
					21–30 cigs/day	6.8 (3.6–12.7)	
					≥ 31 cigs/day	6.9 (3.9–12.4)	
				4–6.9 oz/day	Nonsmoker	1.2 (0.4–3.7)	
					Former smoker	3.1 (1.9–5.2)	
					1–20 cigs/day	5.9 (3.5–10.0)	
					21–30 cigs/day	15.8 (7.4–33.8)	
					≥ 31 cigs/day	18.8 (10.0–35.4)	
				≥ 7 oz/day	Nonsmoker	2.9 (1.1–8.1)	
					Former smoker	5.1 (3.3–7.8)	
					1–20 cigs/day	11.9 (7.7–18.4)	Test for interaction: chi-squared with 12 degrees of freedom = 24.6, $p = 0.02$
					21–30 cigs/day	13.5 (7.9–23.2)	
					≥ 31 cigs/day	20.1 (12.9–31.5)	
				Women			
				Nondrinker	Nonsmoker	1.0	
					Former smoker	1.3 (0.9–2.0)	
					1–20 cigs/day	2.9 (1.9–4.3)	
					≥ 21 cigs/day	3.8 (2.3–6.2)	
				1–3.9 oz/day	Nonsmoker	0.7 (0.3–1.4)	
					Former smoker	2.1 (1.2–3.8)	
					1–20 cigs/day	5.8 (3.5–9.8)	
					≥ 21 cigs/day	22.3 (9.6–51.8)	
				≥ 4 oz/day	Nonsmoker	3.5 (0.9–13.4)	
					Former smoker	2.7 (0.95–7.9)	
					1–20 cigs/day	17.6 (8.1–37.5)	Test for interaction: chi-squared with 6 degrees of freedom = 18.7, $p = 0.005$
					≥ 21 cigs/day	26.7 (12.3–58.6)	

Table 2.3.9 (contd)

Reference	Place, year	Study population	Definition of tobacco/alcohol exposure	Alcohol categories	Smoking categories	Relative risk (95% CI)	Comments
André *et al.* (1995)	Doubs region, France, 1986–89	Cases: 299 men ≥ 35 years old (oral cavity, oropharynx and larynx) Controls: 645 men, population controls ≥ 35 years old	Tobacco: g of tobacco/day	0–40 g/day	0–7 g/day	1	Logistic regression model; risk estimates adjusted for age and environment [no formal test for interaction]
					8–19 g/day	7.1 (1.9–26.1)	
					≥ 20 g/day	10.9 (2.9–40.8)	
				41–100 g/day	0–7 g/day	4.9 (1.3–18.2)	
					8–19 g/day	25.3 (7.7–82.9)	
					≥ 20 g/day	42.8 (13.1–140)	
				> 100 g/day	0–7 g/day	62 (12.2–316)	
					8–19 g/day	194 (49.4–760)	
					≥ 20 g/day	199 (56.5–699)	
Muscat *et al.* (1996)	New York, Illinois, Michigan, Pennsylvania, 1981–90	Cases: 697 men, 322 women (oral neoplasia) Controls: 619 men, 304 women, hospital controls, matched on gender, age, race and date of admisssion	Tobacco: cumulative tar	*Men*			Reference category was never-smokers for all drinking categories. Logistic regression model; estimates adjusted for age and education; further modelling of data revealed a significant interaction between smoking and alcohol consumption for both men and women. [No formal test for interaction presented]
				0 to < 1 drink/week	< 1.4 kg	0.7 (0.3–1.8)	
					1.4–3.5 kg	0.3 (0.1–1.1)	
					> 3.5–6.8 kg	1.0 (0.5–2.6)	
					> 6.8 kg	1.0 (0.4–2.8)	
				Occasional drinker	< 1.4 kg	0.9 (0.3–2.3)	
					1.4–3.5 kg	0.5 (0.2–1.5)	
					> 3.5–6.8 kg	1.2 (0.4–3.7)	
					> 6.8 kg	1.6 (0.6–4.7)	
				1–4 drinks/day	< 1.4 kg	1.0 (0.4–2.1)	
					1.4–3.5 kg	1.5 (0.7–3.2)	
					> 3.5–6.8 kg	1.8 (0.8–3.8)	
					> 6.8 kg	2.5 (1.1–5.2)	
				> 4 drinks/day	< 1.4 kg	2.1 (0.7–5.9)	
					1.4–3.5 kg	2.7 (1.1–6.6)	
					> 3.5–6.8 kg	4.7 (2.0–11.3)	
					> 6.8 kg	6.1 (2.6–14.4)	
				Women			
				0 to < 1 drink/week	< 1.4 kg	1.2 (0.6–2.4)	
					1.4–3.5 kg	3.0 (1.3–7.0)	
					> 3.5–6.8 kg	2.0 (1.0–4.0)	
					> 6.8 kg	2.4 (0.8–6.9)	
				Occasional drinker	< 1.4 kg	1.4 (0.5–4.3)	
					1.4–3.5 kg	1.2 (0.4–3.6)	
					> 3.5–6.8 kg	5.8 (1.7–20.3)	
					> 6.8 kg	16.7 (1.8–152.6)	
				1–4 drinks/day	< 1.4 kg	5.9 (1.7–20.5)	
					1.4–3.5 kg	9.5 (2.8–32.0)	
					> 3.5–6.8 kg	14.0 (4.1–48.5)	
					> 6.8 kg	18.6 (4.0–86.8)	
				> 4 drinks/day	< 1.4 kg	1.0 (0.01–27.9)	
					1.4–3.5 kg	4.3 (0.1–116.9)	
					> 3.5–6.8 kg	6.5 (0.1–174.2)	
					> 6.8 kg	2.4 (0.0–55.1)	

Table 2.3.9 (contd)

Reference	Place, year	Study population	Definition of tobacco/alcohol exposure	Alcohol categories	Smoking categories	Relative risk (95% CI)	Comments
Lewin *et al.* (1998)	Sweden, 1988–90	Cases: 605 men (squamous-cell carcinoma of the head and neck) Controls: 756 men, population controls		< 10 g/day	Nonsmoker	1.0	Logistic regression model; risk estimates adjusted for age and health care area; joint effect of high alcohol intake and current smoking is nearly multiplicative. [No formal test for interaction]
					Former smoker	2.4 (1.4–4.1)	
					Current smoker	6.3 (3.7–10.5)	
				10–19 g/day	Nonsmoker	1.2 (0.5–3.1)	
					Former smoker	2.2 (1.2–4.1)	
					Current smoker	10.4 (5.9–18.3)	
				≥ 20 g/day	Nonsmoker	4.2 (1.8–9.7)	
					Former smoker	5.4 (2.8–10.2)	
					Current smoker	22.1 (13.0–37.8)	
Cohort study							
Chyou *et al.* (1995)	Hawaii, USA 1965–68	American Men of Japanese Ancestry Study (see Section 2.1.1) 92 incident cases of cancer of the upper aerodigestive tract		Non-drinker	Nonsmoker	1.0	Proportional hazards regression model; risk estimates adjusted for age; none of the tests for interaction were statistically significant ($p > 0.05$).
					≤ 20 cigs/day	3.0 (0.8–11.3)	
					> 20 cigs/day	3.2 (0.8–13.4)	
				< 14 oz/month	Nonsmoker	1.3 (0.3–6.3)	
					≤ 20 cigs/day	1.9 (0.5–7.7)	
					> 20 cigs/day	4.6 (1.2–17.8)	
				≥ 14 oz/month	Nonsmoker	6.5 (1.7–26.0)	
					≤ 20 cigs/day	10.7 (3.2–35.4)	
					> 20 cigs/day	14.4 (4.4–47.4)	
					Duration		
				Non-drinker	Nonsmoker	1.0	
					< 30 years	2.0 (0.4–8.8)	
					≥ 30 years	4.2 (1.1–15.5)	
				< 14 oz/month	Nonsmoker	1.3 (0.3–6.3)	
					< 30 years	2.4 (0.6–9.7)	
					≥ 30 years	3.3 (0.9–12.6)	
				≥ 14 oz/month	Nonsmoker	6.5 (1.6–25.9)	
					< 30 years	9.2 (2.7–31.9)	
					≥ 30 years	14.2 (4.4–46.3)	
Liver							
Austin *et al.* (1986)	Alabama, Florida, Massachussetts, North Carolina, Pennsylvania, USA	Cases: 85 cases Controls: 159 hospital controls, matched on gender, age and race		*HBsAg-negative subjects*: Nondrinker	Nonsmoker	1.0	Logistic regression model; information not provided on HBsAg-positive subjects. Test for interaction not statistically significant ($p = 0.50$)
					Former smoker	1.0	
					Current smoker	1.1	
				Occasional drinker	Nonsmoker	1.3	
					Former smoker	1.6	
					Current smoker	4.7	
				Regular drinker	Nonsmoker	3.2	
					Former smoker	1.0	
					Current smoker	3.4	

Table 2.3.9 (contd)

Reference	Place, year	Study population	Definition of tobacco/alcohol exposure	Alcohol categories	Smoking categories	Relative risk (95% CI)	Comments
Chen *et al.* (1991)	China, Province of Taiwan, 1985–87	Cases: 200 incident cases (men) Controls: 200 population controls		Not habitual drinker	Nonsmoker	1.0	Logistic regression model; interaction between smoking and drinking not significant under the multiplicative model [numbers not provided]
					1–10 cigs/day	1.0	
					11–20 cigs/day	1.8	
					> 20 cigs/day	2.7	
				Habitual drinker	Nonsmoker	2.9	
					1–10 cigs/day	3.2	
					11–20 cigs/day	6.2	
					> 20 cigs/day	11.7	
Yu *et al.* (1991)	Los Angeles County, USA, 1984–90	Cases: 74 incident cases Controls: 162 population controls		≤ 29 drink–years	Nonsmoker	1.0	Logistic regression model [no formal test for interaction]
					Former smoker	1.4 (0.3–6.0)	
					Current smoker	3.7 (0.9–15.5)	
				≥ 30 drink–years	Nonsmoker	4.2 (0.8–22.2)	
					Former smoker	4.8 (1.3–17.4)	
					Current smoker	5.4 (1.4–21.0)	
Tanaka *et al.* (1992)	Fukuoka, Japan, 1985–89	Cases: 168 men, 36 women Controls: 291 men, 119 women, hospital controls, frequency-matched on age and sex All subjects aged 40–69 years		< 9.8 drink–years	< 18.4 pack–years	1.0	Logistic regression model; risk estimates adjusted for sex, age, HBsAg status, history of blood transfusion and family history. Lowest drinking category used as reference. [No formal test for interaction]
					18.4–31.9 pack–years	1.0	
					≥ 32 pack–years	1.0	
				9.8–54.1 drink–years	< 18.4 pack–years	0.8	
					18.4–31.9 pack–years	1.2	
					≥ 32 pack–years	1.0	
				≥ 54.2 drink–years	< 18.4 pack–years	0.8	
					18.4–31.9 pack–years	2.1	
					≥ 32 pack–years	1.8	

Table 2.3.9 (contd)

Reference	Place, year	Study population	Definition of tobacco/alcohol exposure	Alcohol categories	Smoking categories	Relative risk (95% CI)	Comments
Mukaiya *et al.* (1998)	Sapporo, Japan, 1991–93	Cases: 104 men Controls: 104 men, hospital controls, matched on age	Alcohol: Nondrinker and ex-drinker for ≥ 10 years Current drinker and ex-drinker for < 10 years	Nondrinker Current drinker	Nonsmoker Former smoker Current smoker Nonsmoker Former smoker Current smoker	1.0 9.4 15.4 *p* for trend = 0.006 9.8 17.3 17.9 *p* for trend = 0.29	Stratified analysis [no formal test for interaction]
Kuper *et al.* (2000)	Athens, Greece, 1995–98	Cases: 333 incident cases Controls: 360 hospital controls		0–40 glasses/week ≥ 40 glasses/week	Nonsmoker < 3 packs/day ≥ 2 packs/day Nonsmoker < 3 packs/day ≥ 2 packs/day	1.0 2.1 (1.0–4.6) 1.7 (0.6–5.3) 4.2 (0.7–25.9) 2.4 (0.9–6.9) 10.9 (3.5–33.8)	Logistic regression model; risk estimates adjusted for age, gender, years of schooling and coffee drinking. Strong, statistically significant ($p = 0.0001$) and apparently super-multiplicative interaction between heavy smoking and heavy drinking in the causation of hepatocellular carcinoma. Effect stronger in HBV and/or HCV negative subjects, further confirmed by case–case analysis

Table 2.3.10. Studies on interaction of smoking and hepatitis B in the causation of cancer of the liver

Reference	Place, year	Study population	HBsAg categories	Smoking categories	Relative risk	Comments
Trichopoulos *et al.* (1987)	Athens, Greece, 1976–84	Cases: 194 incident hepatocellular carcinoma cases Controls: 456 hospital controls	HBsAg– subjects	Nonsmoker Former smoker 1–9 cigs/day 10–19 cigs/day 20–29 cigs/day ≥ 30 cigs/day	1.0 2.8 0.8 2.0 2.4 7.3	Logistic regression model; risk estimates adjusted for age, sex, and alcohol consumption [nonsmokers used as reference group for both HBsAg subgroups]
			HBsAg+ subjects	Nonsmoker Former smoker 1–9 cigs/day 10–19 cigs/day 20–29 cigs/day ≥ 30 cigs/day	1.0 1.3 1.2 2.2 1.2 2.0	
Chen *et al.* (1991)	China, Province of Taiwan, 1985–87	Cases: 200 incident cases (men) Controls: 200 population controls	HBsAg–, HBeAg–	Nonsmoker 1–10 cigs/day 11–20 cigs/day > 20 cigs/day	1.0 1.2 2.0 2.4	Stratified analysis [no formal test for interaction]
			HBsAg+, HBeAg–	Nonsmoker 1–10 cigs/day 11–20 cigs/day > 20 cigs/day	15.1 13.6 44.6 68.1	
			HBsAg+, HBeAg+	Nonsmoker 1–10 cigs/day 11–20 cigs/day > 20 cigs/day	27.8 107.0 206.9 197.6	

Table 2.3.11. Studies on interaction of human papillomavirus (HPV) and smoking in the causation of cancer of the cervix

Reference	Study type	Place, year	Study population	HPV exposure	Smoking categories	Relative risk (95% CI)	Comments
Basu *et al.* (1991)	Cross-sectional study	New York, USA	75 women referred to a colposcopy clinic for abnormal Pap smear		Smoker HPV-positive	Cases vs non-cases (%) 53.5 *vs* 36.7 66.7 *vs* 53.3	Difference not statistically significant. Discrepancies between text and table for percentage of HPV-positive women among non-cases
Ylitalo *et al.* (1999)	Nested case–control (see Table 2.1.10.6)	Uppsala County, Sweden, 1965–95	Cohort: ~ 281 000 women Cases: 422 patients diagnosed with cervical carcinoma *in situ* Controls: 422 controls, matched on date of entry into cohort and birth year	HPV 16/18 DNA negative before diagnosis (n = 138)	Nonsmoker Former smoker Current smoker 1–9 years of smoking 10–19 of smoking ≥ 20 of smoking 0.15–3.95 pack–years 4.00–7.95 pack–years ≥ 8.00 pack–years	1.0 1.5 (0.7–3.4) 1.8 (0.9–3.6) 1.5 (0.7–3.4) 1.7 (0.8–3.5) 2.0 (0.7–5.9) 1.4 (0.7–2.9) 2.7 (1.2–6.4) 1.6 (0.7–3.5)	Logistic regression models. Risk estimates adjusted for education, marital status, oral contraceptive use, age at sexual debut, number of sexual partners, age at menarche and parity. [No formal test for interaction]
				HPV 16/18 DNA positive before diagnosis (n = 178)	Nonsmoker Former smoker Current smoker 1–9 years of smoking 10–19 years of smoking ≥ 20 years of smoking 0.15–3.95 pack–years 4.00–7.95 pack–years ≥ 8.00 pack–years	1.0 2.1 (1.04–4.3) 2.3 (1.3–4.3) 2.3 (1.1–5.2) 2.5 (1.3–4.7) 1.8 (0.8–4.1) 2.3 (1.1–4.8) 3.4 (1.6–7.3) 1.6 (0.8–3.2)	
Kjellberg *et al.* (2000)	Case–control	Northern Sweden, 1993–95	Cases: 137 women with high grade CIN Controls: 253 healthy population-controls, matched on age	HPV Ab–	Never-smoker Ever-smoker	1.0 5.6 (2.5–10.9)	Risk estimates adjusted for age [although matched on age]. No evidence of interaction. [No numbers provided]
				HPV Ab+	Never-smoker Ever-smoker	5.2 (2.5–10.9) 10.5 (5.0–22.4)	

Table 2.3.11 (contd)

Reference	Study type	Place, year	Study population	HPV exposure	Smoking categories	Relative risk (95% CI)	Comments
Hildesheim *et al.* (2001)	Cross-sectional	Costa Rica, 1993–94	Population: 989 HPV positive women Cases: 146 prevalent high-grade squamous intraepithelial lesions or cervical cancer Controls: women with or without low grade squamous intraepithelial lesions	All HPV positive	Never-smoker Former smoker Current smoker < 10 years smoking ≥ 10 years smoking 1–5 cigs/day ≥ 6 cigs/day	1.0 2.4 (1.2–5.1) 2.3 (1.3–4.3) 2.6 (1.2–5.3) 2.2 (1.2–4.2) 2.3 (1.3–3.9) 2.7 (1.1–6.7) *p* for trend = 0.0007	Logistic regression model. Risk estimates for overall analysis adjusted for age, HPV type, number of pregnancies and number of cigarettes/day. Risk estimates for high-risk analysis adjusted for age, number of pregnancies and number of cigarettes/day. No association was found between smoking habit of husband/live-in partner and high-grade squamous intraepithelial lesions/cancer among nonsmoking women. HPV testing for 44 different HPV types.
				High risk HPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68)	Never-smoker Former smoker Current smoker < 10 years smoking ≥ 10 years smoking 1–5 cigs/day ≥ 6 cigs/day	1.0 1.7 (0.8–4.0) 2.3 (1.2–4.3) 2.2 (1.0–4.8) 2.0 (1.0–3.8) 1.8 (0.99–3.3) 3.1 (2.2–7.9) *p* for trend = 0.003	

Table 2.3.12. Studies on the combined effect of tobacco smoking and silica exposure in the causation of lung cancer

Reference	Study design	Country, years of study	Source population	No. of cases and controls	Smoking categories (highest *vs* lowest exposure)	Silica exposure	Relative risk		Interaction[a]	Comments
							Non-smoker	Smoker		
Forastiere *et al.* (1986)	Retrospective case–control	Italy, 1968–84	Male residents in region with pottery industry	72 deaths, 319 controls	Cigarettes per day 0; 1–20; > 20	Ceramic workers without silicosis with silicosis	1.5 0	4.1 1.8	~ M (> M)	Deceased cases and controls; all silicotics were ceramic workers.
Mastrangelo *et al.* (1988)	Case–control	Italy, 1978–80	Workers in quarrying and tunnelling	309 cases, 309 controls	Nonsmoker Ever–smoker	No silicosis Silicosis	1.3 5.3	0.9 1.7	~ A ~ A	Unadjusted analysis
Hessel *et al.* (1990)	Case–control	South Africa, 1975–79	Miners, mainly in gold mines, with silicosis	231 deaths, 318 controls	Cigarettes per day 0; 1–10; 11–20; ≥ 21	Hilar gland silicosis Parenchymal silicosis	1.1 1.6	0.8 0.9	(< A) (< A)	Unmatched odds ratios
Siemiatycki *et al.* (1990)	Case–control	Canada, 1979–85	Male residents of Montreal, aged 35–70 years	479 cases, 875 controls	Pack–years 0; 1–< 30; 30–< 60; ≥ 60	Substantial	2.6	1.5	I	Adenocarcinoma excluded; silica exposure estimated from job titles; adjusted for age, socio-economic status, job history, education, marital status and asbestos exposure
Chiyotani *et al.* (1990)	Cohort	Japan, 1979–83	3335 patients with pneumoconiosis qualifying for workmen's compensation (58% silicotics)	60 deaths	Nonsmoker Former smoker Current smoker	Pneumoconiosis	1.8	6.1	(> M)	
Amandus & Costello (1991)	Cohort	USA, 1959–75	9912 metal miners; white males	132 deaths	Nonsmoker Former smoker Current smoker	Silicosis Silicosis in low radon mines	2.2 5.1	1.3 1.7	~ A (~ A)	Adjusted for age; 'interaction between silicosis and cigarette smoking habits not a statistically significant factor related to lung mortality'
Hnizdo & Sluis-Cremer (1991)	Cohort	South Africa, 1968–86	2132 white gold miners with silicosis, aged 45–54 years	77 deaths	Pack–years ≥ 26 *vs* ≤ 25	≥ 31 *vs* ≤ 30 dust particle–years	1.4	1.9		'Combined effect of dust and smoking is more than additive.'

Table 2.3.12 (contd)

Reference	Study design	Country, years of study	Source population	No. of cases and controls	Smoking categories (highest *vs* lowest exposure)	Silica exposure	Relative risk		Interaction[a]	Comments
							Non-smoker	Smoker		
Amandus *et al.* (1991)	Cohort	USA, 1940–83	760 silicotics among dusty trades workers	33 deaths	Never-smoker Ever-smoker	Silicosis	SMR 1.7	SMR 3.4	(> M)	Standardized mortality ratios using US male population as reference group
Chia *et al.* (1991)	Cohort	Singapore, 1970–84	159 granite workers with silicosis	9 cases	Nonsmoker Smoker	Silicosis	1.3	2.2	(> M)	
Hnizdo *et al.* (1997)	Nested case–control	South Africa, 1970–86	2260 white gold miners, aged 45–54 years	78 cases, 386 controls	Pack–years: < 10; 10–29; ≥ 30	Without silicosis With silicosis	1.0 4.1	11.7 48.9		'Strong multiplicative combined effect of smoking and the presence of silicosis on the risk of lung cancer'
Hughes *et al.* (2001)	Nested case–control	USA, 1940–84	2670 male industrial sand workers	123 deaths, 219 controls	Nonsmoker Ever-smoker					'No indication of an interaction effect of cigarette smoking and cumulative exposure'

Adapted from Saracci & Boffetta (1994)

[a] Numbers in parentheses are based on the assumption that the relative risk due to smoking is 10; A, additive; I, intermediate; M, multiplicative

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