Interaction Between Tobacco Smoking and Occupational Exposures in the Causation of Lung Cancer

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The nature of the interaction between smoking and occupational exposure is controversial, in part because of lack of agreement on the definition of interaction and in part because of the scarcity of adequate epidemiologic data. Occupational investigators have assessed interaction primarily as a departure from an additive rather than from a multiplicative model of relative risks (or rate ratios). To determine whether smoking modifies the effect of occupational lung carcinogens, the literature was reviewed for the only four established occupational lung carcinogens for which there are data on smoking: radon daughters, asbestos, arsenic, and chloromethyl ethers. Where possible, departure was assessed from both an additive (synergism) and a multiplicative model (effect modification). Only nine studies were considered to have sufficient sample size and to provide sufficient information on tobacco use and occupational exposure to evaluate interaction. The existing data were contradictory for three of the agents studied: asbestos, radon daughters, and arsenic. Inconclusive or contradictory findings may result from small sample size or lack of comparability of the level of occupational or tobacco exposure. It is noteworthy that, for these four agents, whenever smoking did modify the effect of occupational exposure, the lung cancer rate ratio was greater for nonsmokers (compared to nonexposed nonsmokers) than smokers (compared to nonexposed smokers). However, with the exception of chloromethyl ethers, absolute lung cancer rates were higher for smokers than nonsmokers, regardless of occupational exposure.

U ntil recently, discussions about the nature of the interaction between multiple environmental agents in causing disease have been plagued by semantic prob-

lems. There has been considerable confusion about the meaning of the terms "interaction," "effect modification," and "synergism." Several authors[1-6] have attempted to clarify these concepts by defining them statistically. Despite such clarification, a review of the published occupational literature still encounters wide variation in the use of these terms.

Statistically, the presence or absence of interaction is model-dependent. Depending on what type of model is chosen to represent the combined action of two risk factors (eg, smoking and an occupational agent), a given set of data may be said to "fit" either an additive or a multiplicative model of relative risks (interaction absent), or, conversely, may "depart from" such a model (interaction present). Occupational investigators, wishing to assess the public health importance of a particular agent, have traditionally assessed interaction as a departure from an additive model, whereas epidemiologists interested in etiology have primarily assessed interaction as a departure from a multiplicative model.

The language used to discuss statistical interaction is not intuitive, because it focuses on departure from a statistical model, rather than on the underlying implications of the model itself. Kleinbaum et al[7] have observed that whether one uses an additive or a multiplicative model to assess interaction depends upon the purpose of the assessment. Departure from an additive model carries certain public health implications. Such a departure means that the combined effect of exposure to two (or more) agents is greater than the sum of the separate effects. The elimination of either exposure would be particularly effective in reducing disease occurrence. The implications of departure from a multiplicative model are less intuitive. Such a departure is synonymous with effect modification, meaning that the relative effect of one risk factor (eg, occupation) on disease occurrence is modified by the effect of another

(eg, smoking). Recognition of effect modification can provide important clues about disease etiology.

The purpose of this paper is to review the literature on the interaction between tobacco smoking and four established lung carcinogens: asbestos, radon daughters, arsenic, and chloromethyl ethers.

The term "synergism" will be avoided in this review. Although commonly taken to mean departure from an additive model of relative risks (or rate ratios or odds ratios), this term has also been used to describe interaction at a biochemical or cellular level.[7] To avoid confusion, we will here confine our review to an assessment of interaction defined as departure from an additive or multiplicative model of relative risks.

We preface the review with a brief description of the criteria used to assess interaction, illustrated by two examples.

Definitions and Examples

If RR_a and RR_b are the rate ratios (relative risk, odds ratio) due to agent "a" alone and agent "b" alone, while RR_{ab} is the rate ratio due to both agents in reference to a population exposed to neither, then departure from an additive scale may be defined as RR_{ab} being not equal to $(RR_a + RR_b - 1)$, while departure from a multiplicative scale may be defined as RR_{ab} being not equal to $RR_a \times RR_b$.[19]

In a stratified analysis of categorical data, the point estimates of RR_a and RR_b can be added or multiplied directly and compared to RR_{ab} to determine whether an additive or multiplicative model best fits the data. Significance testing can be done if the variance of the estimates is known.

Departure from a multiplicative model can also be recognized by the presence of effect modification, or the nonuniformity of RR_a across strata, after stratification of the data by agent "b." Such nonuniformity is mathematically equivalent to departure from a multiplicative model, and again can be tested for significance if the variance of the point estimates is known.

Finally, some investigators choose to create mathematical models with their data, usually using continuous data. In this case, departures from an additive or multiplicative model can be assessed by testing the significance of an interaction term ($RR_a \times RR_b$) in either model.

Tables 1 and 2 illustrate the definitions discussed above with examples from hypothetical studies of lung cancer mortality among workers exposed to agent X and agent Y. In each of these hypothetical studies, 10,000 workers were followed for 10 years, and in each study half were exposed while half were nonexposed.

In our review of studies assessing the interaction between smoking and occupation, we will focus on lung cancer and its association with radon daughters, asbestos, arsenic, and chloromethyl ethers. A summary of the results for all studies reviewed is provided by Table 12.

TABLE 1

Interaction as a Departure from Additive Model in a Hypothetical Example for Lung Cancer, Smoking, and Agent X*

	Nonsmokers (n = 5,000) Agent X		Smokers (n = 5,000) Agent X	
	−	+	−	+
Lung cancer deaths	1	2	10	20
Person-years	25,000	25,000	25,000	25,000
Death rate/10^5	4	8	40	80
Rate ratio for agent X/not agent X	2 (nonsmokers)		2 (smokers)	

* RR (rate ratio) for smoking alone = 10; RR for agent X alone = 2; RR for smoking and agent X together = 20; RR expected for smoking and agent X under additive model = 11 (10 + 2 − 1); effect modification absent (no change in RR over smoking strata).

TABLE 2

Interaction as a Departure from Multiplicative Model in a Hypothetical Example for Lung Cancer, Smoking, and Agent Y*

	Nonsmokers (n = 5000) Agent Y		Smokers (n = 5000) Agent Y	
	−	+	−	+
Deaths	1	10	10	20
Person years	25,000	25,000	25,000	25,000
Death rate/10^5	4	40	40	80
Rate ratio for agent Y/not agent Y	10 (nonsmokers)		2 (smokers)	

* RR (rate ratio) for smoking alone = 10; RR for agent Y alone = 10; RR for smoking and agent Y together = 20; RR expected in multiplicative model for smoking and agent Y = 100 (10 × 10); effect modification present (change in RR over smoking strata).

TABLE 3

Asbestos Studies with Smoking Information

Reference No.	Population	Design
8	New York insulation workers	Cohort (external referent)
9	English asbestos workers	Cohort (external referent)
11	US insulation workers	Cohort (external referent)
12	US asbestos factory workers	Cohort (external referent)
13	Canadian mine/mill workers	Nested case-control
10	English asbestos workers	Cohort (external referent)
15	English asbestos workers	Cohort (external referent)

Asbestos

There have been a number of studies of asbestos-exposed workers where smoking data are available. These studies are summarized in Table 3. The 1968 study by Selikoff et al[8] and the 1972 study by Berry et al[9] were small studies in which no lung cancer deaths were observed among nonsmoking males, and virtually none were expected. The 1984 study by Acheson et al[10] has only one observed lung cancer among nonsmokers, and the expected deaths are not calculated using smoking-specific lung cancer rates. It is impossible to draw quantitative conclusions from these studies, and we will not review them here.

In a study with much more data, Hammond et al[11] followed 12,051 male insulators with at least 20 years

of asbestos exposure from 1967 to 1976. Although no data are presented as to the type of asbestos used in insulation, Selikoff et al[12] have commented that insulation workers originally were exposed primarily to chrysotile asbestos, but later were exposed to both chrysotile and amosite.

The mortality pattern of these workers was compared with that of 73,763 male blue-collar workers who were enrolled in a prospective study conducted by the American Cancer Society and followed from 1967 to 1972. Smoking habits of 68% of the exposed were obtained by mailed questionnaire in 1966; of these, 11% had never smoked, 6% had smoked only a pipe and cigar, and 83% were current or ex-smokers of cigarettes. Smoking-specific analyses divided the exposed into smokers (current and ex-smokers of cigarettes) v nonsmokers (never smoked). Smoking-specific lung cancer death rates were calculated, age-standardized to the entire exposed population. The results for those with known smoking habits are shown in Table 4. Given that the rate ratio for asbestos changes little over smoking strata, there is no effect modification, and hence no interaction as defined as a departure from a multiplicative model. However, given that there were only four deaths among nonsmoking asbestos workers, the variance of the rate ratio among nonsmokers is quite large, and firm conclusions are impossible.

In contrast, the studies of Liddell et al,[13] Selikoff et al,[12] and Berry et al[15] suggest that tobacco smoking may modify the effect of asbestos exposure.

Liddell et al[14] have provided the most recent and thorough analysis of smoking and lung cancer among Quebec miners and millers of asbestos (previously analyzed by Liddell et al[13] and McDonald et al.[16] This cohort is composed of 10,939 men exposed to chrysotile asbestos during mining and milling in Quebec. These men were followed from 1926 to 1975. Smoking histories were obtained in 1970 for 93% of the dead (via next-of-kin) who died after 1950 (only about 800 of 4,463 male deaths occurred before 1950), and from 100% of the living. After excluding men without known smoking habits, 223 lung cancer case subjects were studied in a nested case-control study. Three control subjects were chosen per case subject, after being matched for date of birth and

smoking habit. Exposures occurring later than 9 years before the death of the case subject or his matched control subject were ignored.

The authors presented both the unmatched data (Table 5), as well as the results from fitting additive and multiplicative models with the matched data. Results were similar for matched and unmatched data. The authors considered that exposures to less than 100 fibers per milliliter-years caused little or no increased risk of lung cancer, and defined men with such slight exposures as nonexposed. According to the unmatched data, non-smokers exposed to more than an accumulated 100 fibers per milliliter-years had an odds ratio of 2.98 (95% confidence interval [CI] 1.17 to 7.60) compared to those who had less than 100 fibers per milliliter-years. Among cigarette smokers those exposed to more than 100 fibers per milliliter-years had an odds ratio of 1.66 (95% CI 1.19 to 2.33) compared to cigarette smokers who were exposed to less than 100 fibers per milliliter-years. Although the point estimates differ, the overlapping confidence intervals make it impossible to conclude that nonsmokers have a higher ratio of asbestos-induced lung cancer than do smokers, when compared to their respective lesser-exposed referent groups.

The authors then fitted a model to the matched data to assess interaction. They found that both an additive and multiplicative model fit the data, although the fit of the multiplicative model was slightly better. They concluded that the combined effect of smoking and asbestos on the rate ratio for lung cancer was somewhere between additive and multiplicative.

In a 1980 publication, Selikoff et al[12] did find that smoking changed the rate ratio for asbestos exposure. These authors studied a cohort of 582 men with at least 20 years of potential latency who worked in an asbestos factory using exclusively amosite asbestos. These men began working from 1941 to 1945 and were followed through 1977. Smoking data were collected from them beginning in 1961. Of the 582, 430 (74%) were regular cigarette smokers, whereas 137 (26%) had never smoked or smoked only pipes and cigars. Expected rates of death from lung cancer were derived from the smoking-specific death rates of blue-collar workers in the large prospective study of smokers conducted by the American Cancer Society. The results are shown in Table 6.

The data in Table 6 would indicate that nonsmokers have a higher rate ratio than smokers when compared to their respective smoking-specific referent groups.

TABLE 4

Lung Cancer Death Rates (from Hammond et al[11])

| | Nonsmokers Asbestos | | Smokers Asbestos | |
	−	+*	−	+
Deaths	NA	4.0	NA	268.0
Person-years	NA	6849	NA	45,401
Death rate/100,000	11.3	58.4	120.2	590.3
Rate ratio	5.17 (1.40–13.3)†		4.91 (4.34–5.54)	

* Death rates among nonasbestos workers are those of white males in blue collar occupations (n = 74,000) from the American Cancer Society study.[37] There were 891 nonsmokers and 6,841 smokers in the exposed groups. All exposed workers had 20 years since first employment.
† 95% confidence intervals were calculated assuming comparison rates were invariate.

TABLE 5

Lung Cancer Case-Control Study (from Liddell et al[13])

| Fibers | Nonsmokers (n = 224) | | Smokers (n = 714) | |
	<100 Fibers*	>100 Fibers	<100 Fibers	>100
Cases	6	17	69	131
Controls	103	98	240	274
Odds ratio	2.98 (1.17–7.60)		1.66 (1.19–2.33)	

* "Fibers" refers to cumulative fibers per milliliter-years of exposure to chrysotile asbestos.

The approximate confidence intervals presented in Table 6, based on the assumption that comparison rates are invariate, would indicate that these rate ratios are significantly different. Hence, these data would suggest that an interaction defined as departure from a multiplicative model is occurring and that nonsmokers have a higher rate ratio of lung cancer due to asbestos than do smokers, when compared to the appropriate referent group.

Berry et al[15], expanding on an earlier study, have followed 1,250 male and 420 female asbestos factory workers (type of asbestos not reported). Smoking habits were determined in 1971 for 81% of the cohort which had been defined at that time (smokers, ex-smokers, and never smokers, with ex-smokers not defined). The population of London was used as a comparison group, and expected numbers of deaths were adjusted by factors representing the effects of different smoking habits on lung cancer mortality. These factors were derived from known relative risks for smokers,[17] and known smoking habits of the British population. Both men and women were analyzed. Results (shown in Table 7) for men and women combined showed that nonsmokers had the highest rate ratio for lung cancer death, followed by ex-smokers, and then smokers, although differences between groups were not always significant due to sample size.

In summary, then, the study by Hammond et al[11] suggests that smoking does not modify the effect of asbestos, although small numbers allow no firm conclusion (no interaction on a multiplicative scale). The Liddell data[13] could support a finding that the rate ratio

due to exposure to asbestos and smoking is somewhere between additive and multiplicative. Finally, the data by Selikoff et al[12] and Berry et al[15] indicate that effect modification is occurring, with nonsmokers at higher relative risk than smokers (supporting an additive rather than a multiplicative model). These data are summarized in Table 12. It is possible that the seemingly contradictory findings are merely an artifact of small sample size, or due to different intensities of exposure to asbestos in these cohorts. It is also possible that the different types of asbestos studied interact differently with cigarette smoke. Berry et al[15] reach similar conclusions regarding the existing literature.

Radon Daughters

Miners may be exposed to radon daughters (alpha radiation) via inhalation in uranium or other mines. A number of studies have assessed the association of radon daughter exposure and lung cancer, and have considered the effects of smoking. A list of these studies is shown in Table 8.

Several studies listed in Table 8 include information on the interaction of smoking and occupation, but sample size limitations or lack of well-defined smoking or exposure data make quantitative evaluation difficult. We therefore do not review these studies in detail. However, three of these unreviewed studies suggest a higher rate ratio for lung cancer among nonsmokers than smokers[18,20] compared with smoking-specific nonexposed populations, whereas one suggests equal rate ratios.[21]

TABLE 6

Lung Cancer Mortality Among Asbestos Factory Workers (from Selikoff et al[12])

	Nonsmokers* Asbestos		Smokers Asbestos	
	−	+	−	+
Deaths expected and observed†	0.4 (expected)	7.0 (observed)	9.6 (expected)	45.0 (observed)
Person-years	NA	1,398	NA	4,811
Death rate/100,000	28.6	500.5	199.5	935.8
Rate ratio (asbestos/nonasbestos)	17.50 (7.1–36.1)‡		4.69 (3.42–6.37)	

* Nonsmokers include smokers of pipes and cigars.
† Death rates of nonasbestos workers were derived from lung cancer rates of blue-collar workers.[37] In the exposed population there were 430 cigarette smokers, and 137 men who never smoked at all or only smoked a pipe or cigar. All workers had been employed for at least 20 years.
‡ 95% confidence intervals were calculated under the assumption that the comparison rates were invariate.

TABLE 7

Lung Cancer Mortality Among Asbestos Factory Workers (from Berry et al[14])

	Nonsmokers Asbestos		Ex-smokers* Asbestos		Smokers Asbestos	
	−	+	−	+	−	+
Deaths expected and observed	0.4 (expected)	4.0 (observed)	2.9 (observed)	13 (observed)	28.6 (expected)	62 (observed)
Person-years	NA	1,596	NA	2,847	NA	9,584
Death rate/100,000	25.1	250.6	102.2	456.6	294.9	646.9
Rate ratio (asbestos/nonasbestos)	10.0 (2.7–25.6)†		4.46 (2.38–7.64)		2.21 (1.68–2.81)	

* Time of quitting not defined.
† 95% confidence intervals were calculated under the assumption that the comparison rates (London rates adjusted for smoking) were invariate.

TABLE 8

Radon Daughter Studies with Smoking Information

Reference	Population	Design
22	White US uranium miners	Cohort (external referent)
24	White US uranium miners	Cohort (internal referent)
20	Swedish zinc/lead miners	Population case-control
19	Swedish iron ore miners	Population case-control
25	White US uranium miners	Nested case-control
18	Navajo US uranium miners	Population case-control
26	Swedish iron ore miners	Cohort (external referent)
21	Swedish iron ore miners	Population case-control

The US uranium miner cohort (described below) is exceptional in that data are available on both exposure (in terms of working-level-months or WLM of alpha radiation) and on smoking for all cohort members. There are no truly nonexposed workers in this group, although there are a number who were exposed to low levels of alpha radiation.

Lundin et al[22] produced the first report on the US uranium miner cohort, which included follow-up from 1950 to 1969. Using smoking-specific white male lung cancer rates as reported by Haenszel et al,[23] to generate expected lung cancer deaths among 3,414 white male uranium miners, the authors found that smokers and nonsmokers had similar standard mortality rates (SMRs) for lung cancer (3.87 and 4.00, respectively). However, there were only two nonsmoker lung cancer deaths, limiting the stability of these estimates.

Archer et al[24] analyzed the same cohort with follow-up through 1974. However, their data on smoking and lung cancer do not allow a quantitative assessment of interaction due to the lack of any cumulative exposure category lower than 300 WLM, the lack of age adjustment, and the problem of small numbers.

The analysis by Whittemore and McMillan[25] is the most recent and most thorough analysis of the cohort published to date. Follow-up in their analysis extended through 1977. They have considered 194 white male lung cancer cases, and 776 matched controls. In a nested case-control analysis, the authors chose four control subjects per case subject, matched on birth date. Whittemore and McMillan used cumulative pack-years in determining smoking status. They also cut off the exposure histories of case subjects and their matched control subjects 10 years before the death of the case, on the assumption that such doses were biologically irrelevant.

The regression analysis conducted by Whittemore and McMillan adjusted for the effects of age and calendar time. Such an analysis also had the advantage of using continuous data on smoking and exposure. The model used by the authors assumed that the effects of smoking and exposure were multiplicative, an assumption which was justified in that the multiplicative model fit the data, while the additive model was rejected. They found that when they included an interaction term in the multiplicative model, which would indicate that smoking modified the effect of radon daughters, it was not significant. Hence, there was no interaction in these data, as defined as a departure from a multiplicative model.

The other principal study of radon daughter exposure

and lung cancer, which has smoking data, is based on nonuranium miners in Sweden. This study, conducted by Radford and St. Clair Renard,[26] is a retrospective cohort study of lung cancer mortality from 1951 to 1976 among 1,415 Swedish iron miners. Smoking histories were obtained for 39% of the cohort. The average duration of mining for this cohort was 20 years. After restriction of the cohort to men who had worked at least 10 years underground, the average cumulative dose for these miners was 94 WLM (an order of magnitude lower than the US uranium miners). About one-third of these miners were surface miners, without appreciable exposure.

Overall results showed an excess rate of lung cancer (SMR = 3.42, 50 observed deaths, 14.6 expected, $P <$ .01) for the entire cohort compared to the Swedish population. The excess was confined to underground miners; the surface miners showed no excess. Stratification by WLM dose levels showed an increase in lung cancer rates with increased dose, although this increase was not always consistent.

To calculate smoking-adjusted rate ratios for the miners, Radford and St. Clair Renard used an adjustment of the type suggested by Axelson,[27] in order to calculate expected lung cancers among both smoking miners and nonsmoking miners. Using known rate ratios of lung cancer for smokers v nonsmokers, and known proportions of smokers in the national population, the authors estimated national lung cancer rates for smokers and nonsmokers, adjusted for age and calendar year. These smoking-specific national rates were applied to the person-years of the miners cohort. The estimated fraction of the total person-years for smoking miners compared with nonsmoking miners was based on the two surveys that had yielded smoking data on 39% of the cohort. Smoking-specific expected deaths were then compared with smoking-specific observed deaths (smoking data had been collected for all lung cancer deaths). The average cumulative dose for nonsmokers and smokers was approximately equal (79 and 84 WLM, respectively).

Using these procedures, the authors estimated that the rate ratio for smoking miners was 2.9 (90% CI 2.1 to 3.9, 32 observed deaths/11 expected), and 10.0 for nonsmoking miners (90% CI 6.5 to 14.8, 18 observed/1.8 expected), compared with the national population (Table 9). Given this statistically significant effect modification, there is evidence of interaction as defined as a departure from a multiplicative model. Table 12 shows that these data conform to an additive model.

In summary, the most thorough assessment of white male US uranium miners[25] provides no evidence of a departure from a multiplicative model for the combined risk for lung cancer due to smoking and radon daughters. However, in this analysis there is no truly nonexposed referent group. On the other hand, the other thorough analysis of radon daughter exposure, among iron ore miners in Sweden,[26] indicates that, in fact, an additive model is appropriate. In these data, smoking modified the effect of radon daughters, with nonsmokers having a higher rate ratio than smokers, using the Swedish population as the referent group.

	Nonsmokers* Radon Daughters		Smokers Radon Daughters	
	−	+	−	+
Deaths†	NA	18	NA	32
Person-years (approx)‡	NA	12,426	NA	11,657
Death rate/100,000, person-years	14.5	144.9	99.4	274.5
Rate ratio	10.0 (6.5–14.8)§		2.9 (2.1–3.9)	

* Nonsmokers include former smokers who quit at least 10 years previously. Pipe smokers were considered smokers, based on Swedish data for lung cancer and smoking; 570 men, of a cohort of 1415, were surveyed for smoking habits, and their habits extrapolated to the remainder of the cohort.
† Number of expected deaths among radon-exposed workers computed by applying smoking-age-sex-race specific rates of the Swedish national population to person-years denominators of iron ore miners.
‡ Smoking-specific person-years in this cohort were estimated using data presented in the paper about the age-distribution of the person-years and a formula presented to determine age-specific smoking prevalence rates.
§ 90% confidence interval.

One explanation for these contradictory findings might be that the different doses received by US and Swedish miners led to a different response among smokers and nonsmokers. The Swedish miners received much lower exposures over a longer period of time (an average 4.8 WLM per year over 20 years v 99 WLM per year over 8 years). Alternatively, there may be qualitative differences between doses in the uranium mines and the iron ore mines. Different dust levels can affect the actual dose to the lungs. WLMs do not reflect actual lung dose, but ony the amount of potential alpha energy present in a certain quantity of air. Yet another possibility is that the exposure estimates in the US cohort are inaccurate. There is some reason to believe that the US exposures have been overestimated.[28]

An alternative explanation is that observing a higher rate ratio for nonsmokers may be a function of using a nonmining nonexposed group as the referent group, instead of an internal referent group. An internal referent group of miners may, in fact, have had enough radon daughter exposure to increase "background" lung cancer risk, or may have been exposed to radon daughters or other lung carcinogens (eg, asbestos) while mining in mines other than the one studied. In a yet unpublished study of US miners in which smoking and nonsmoking miners are compared to smokers and nonsmokers in the US population using an Axelson-type of adjustment, preliminary results indicate that non-smoking miners do have a higher rate ratio for lung cancer than smoking miners, paralleling the Swedish results (Robert Roscoe, written communication, June 1985).

Archer et al[24] have postulated that cigarette smoking acts as a promoter, and that smoking miners die of lung cancer with less latency than do nonsmoking miners. Hence, studies with longer follow-up such as the Swedish study, or the more recent follow-up of the US cohort described above, may show an increased risk among nonsmokers. However, the Swedish data indicate that smoking miners (n = 32) who died of lung cancer had approximately the same time-since-first-employment as did nonsmoking miners (n = 18) who died of lung cancer (38.8 years v 41.3 years). Similarly, in the recent follow-up of the US cohort, among those who died of lung cancer the average time-since-first-exposure was 23.0 years for smokers (n = 208) and 25.4 (n = 19) for nonsmokers, scarcely a large difference (personal communication, Robert Roscoe). Furthermore, in the US data the average age-at-first-employment, age-at-death, duration of employment, and WLM dose was similar for smokers and nonsmokers who died of lung cancer. Thus, the Swedish and US data do not appear to offer much support to the hypothesis that smoking shortens the latent period of radon-daughter-induced lung cancer.

Finally, it is worth considering that the investigators in the Swedish study included 10 former smokers among their 18 "nonsmoking" lung cancer cases. Nine of these men had quit smoking at least 25 years before death, and one had quit 18 years before death. Although large prospective studies of smokers do show that former smokers who quit many years previously show little or no excess risk of lung cancer, this situation may not hold in radon-exposed former smokers, especially if the thesis that radon daughters act as promoters is true.

Arsenic

There are four reports on arsenic exposure, smoking, and lung cancer.[29-32] The study by Rencher et al[31] is not reviewed here due to the lack of details presented in the paper on case-ascertainment and on methods used to assess interaction. Nor do we review the study by Welch et al[32] because the smoking-specific analysis stratifies the exposed by smoking but derives expected deaths from a referent group which is not stratified by smoking.

Pinto et al[29] studied 525 retirees of a US copper smelter who had been exposed to arsenic trioxide between 1910 and 1973. Smoking histories were sought from living cohort members in 1961, and for all men dead at that time from relatives. Although the response rate is not noted by the authors, it would appear from the data presented that smoking histories were available for only 377 men. These workers were followed from 1949 to 1973. Although details are not presented in the

paper, expected smoking-specific mortality was derived using an adjustment based on smoking-specific lung cancer rates derived from the Dorn study of US veterans (Vivian Henderson, written communication, January 1985). Results are shown in Table 10. It would appear from these data that nonsmokers have a higher rate ratio, but the differences in rate ratios are not statistically significant (even if the referent group rates are considered invariate, the 95% CI for the SMR for smokers is 1.61 to 4.74, and overlaps the same interval for nonsmokers, which is 1.02 to 14.86). Given that the rate ratios differ between smokers and nonsmokers, these data would indicate that effect modification, or interaction defined as a departure from a multiplicative model, is occurring. On the other hand, the apparent effect modification is not statistically significant, and may be a product of chance.

Pershagen et al[30] conducted a nested case-control study within a cohort of Swedish smelter workers; 3,958 subjects were followed from 1928 to 1977. Of these workers, 953 had died, 76 of lung cancer. Two dead referents were chosen per case from among those who had not died of lung cancer; referents were matched on date of birth with the cases. Company records allowed assessment of arsenic and sulfur dioxide exposure. All workers judged to have been exposed to arsenic had had at least 6 months exposure. Workers were categorized into areas of high (roaster area), medium, and no exposure to arsenic. Certain areas of the smelter were judged to involve no exposure to arsenic; 39% of study subjects were not exposed. Smoking data were obtained by interviewing the next-of-kin of all study subjects, who were divided into smokers (74%) and nonsmokers (26%). There were eight lung cancer cases among nonsmokers.

After stratification by age-at-death, the data show a Mantel-Haenszel adjusted odds ratio of 2.36 (95% CI 0.31 to 17.93) for arsenic exposure among nonsmokers, and an odds ratio of 2.93 (1.40 to 6.14) for arsenic exposure among smokers. The heaviest arsenic exposure was among workers in the roaster area, who were also judged to have low exposure to SO_2. The data presented indicate that among nonsmokers, workers in the roaster area had an odds ratio of 4.4 compared with nonexposed workers, whereas among smokers the odds ratio 4.5. No confidence intervals were presented for these data. Despite the usual instability of estimates due to small

numbers, the data from Pershagen et al suggest that smoking does not modify the effect of arsenic (no interaction on a multiplicative scale).

Chloromethyl Ethers

Weiss[33] has studied a cohort of 51 men with moderate-to-heavy exposure to bis(chloromethyl)ether and chloromethyl methyl ether, collectively referred to as chloromethyl ethers (CME). Smoking habits were ascertained in 1963. Nonsmokers were defined as those who did not smoke or who smoked cigars, or had stopped smoking more than 1 year previously. Nonsmokers and current smokers had approximately the same duration and intensity of exposure. Follow-up was conducted from 1963 to 1972, during which time 11 of these men died of lung cancer. Smoking-specific expected deaths were derived from the large prospective study conducted by Dorn.[34] Results are shown in Table 11. These data show a significantly higher rate ratio for nonsmokers than for smokers, indicating effect modification. Indeed, the rate for nonsmokers is so high that not only do these data indicate interaction as a departure from a multiplicative scale, but also indicate a departure from an additive scale, with the combined effect of smoking and exposure to CME being less than additive. This study is based on an extremely small number of person-years compared with the other studies reviewed here.

Discussion

The data reviewed here comprise nearly all of the information available to assess the interaction between smoking and occupation with respect to lung cancer, yet they are clearly insufficient to support definitive conclusions.

Table 12 summarizes the data reviewed here. Interaction as defined as effect modification, or departure from a multiplicative model, is apparent in two asbestos studies, not apparent in a third, and a fourth is equivocal. For radon daughters there are also contradictory findings; the Swedish data indicate effect modification, whereas the published US data do not. For arsenic,

TABLE 10

Observed and Expected Lung Cancer Deaths Among Arsenic-Exposed Workers (from Pinto et al[29])

Smoking Status	No. of Retirees	Observed Deaths	Expected Deaths*	Smoking-Specific Standard Mortality Rates
Smokers	189	15	5.2	2.87 (1.61–4.76)†
Ex-smokers	69	3	1.2	2.45 (0.49–7.13)
Non-smokers	119	3	0.6	5.06 (1.01–14.61)

* Expected deaths based on Dorn study of veterans.[34]
† 95% confidence intervals were calculated based on the assumption that comparison rates were invariate.

TABLE 11

Lung Cancer Mortality Among Workers Exposed to Chloromethyl Ethers (CME) (from Weiss[33])

	Nonsmokers and Ex-Smokers* CME		Smokers CME	
	−†	+	−	+
Deaths	NA	6	NA	5
Person-years	NA	112	NA	353
Death rate/100,000	19.8	5,357	399.9	1,416
Rate ratio (CME/non-CME)	270.3 (99.5–593.6)		3.5 (1.1–8.3)	

* Ex-smokers includes all who quit smoking for more than 1 year prior to 1963 survey. Also in this category are cigar smokers.
† Smoking-specific death rates of nonexposed were derived from lung cancer rates presented in Ref. 34.

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TABLE 12

Rate Ratios (RR) and Interaction in Nine Studies of Occupation and Lung Cancer Mortality*

	Asbestos				Radon		Arsenic		Chloro-methyl Ethers
	1	2	3	4	5	6	7	8	9
RR nonexposed nonsmoker	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
RR occupation alone	5.2	3.0	17.5	10.0	3.4‡	10.0	5.1	3.0	270.3
RR smoking alone	10.6	4.9	7.0	11.7	4.1‡	17.4	NA	4.9	20.2
Observed RR for both smoking and occupation	52.2	8.2	32.7	25.7	13.9‡	17.7	NA	14.6	71.5
Expected RR for both smoking and occupation in additive model	14.8	6.9	23.5	21.7	7.5‡	16.4	NA	6.9	289.5
Expected RR for both smoking and occupation in multiplicative model	55.1	14.7	122.5	117.4	13.9‡	170.4	NA	14.7	5,460.1
Interaction, departure from additive model	Yes	Maybe§	Slight	No	Yes‡	No	No¶	Yes	Some
Interaction, departure from multiplicative model	No	Maybe§	Yes	Yes	No‡	Yes	Yes¶	No	Yes

* We have used point estimates of rate ratios in this table to assess interaction defined as a departure from an additive or multiplicative model of relative risks. However, there may be wide variations for these point estimates, so that firm conclusions cannot be drawn (see text). Also, ex-smokers have been ignored here, for simplicity's sake.
† Studies 1 to 9 are, respectively, Refs 11, 13, 12, 15, 25, 26, 29, 30, and 33.
‡ Study 5[25] derived its estimates of relative risk (or rate ratios) via modeling. The authors determined that the multiplicative models of relative fit the data better than the additive one. The RRs presented here use the multiplicative model with average levels of cigarette and radon daughter exposure. Given that a multiplicative model is used, the data of course conform to such a model and not an additive one.
§ Although in study 2[13] the authors presented stratified data enabling us to present estimates of rate ratios as indicated, to test for interaction they modeled the data and concluded that the combined relative risk for smoking and asbestos exposure was somewhere in between additive and multiplicative.
¶ Study 7[29] did not present data sufficient to determine the rate ratios for smoking or for arsenic alone, but presented only summary rate ratios for exposed smokers and exposed nonsmokers. The effect modification seen in the point estimates of these rate ratios is the basis for our decision to categorize these data as suggesting a departure from the multiplicative model.

Pinto et al[29] suggest effect modification; Pershagen et al[30] do not. Finally, for CME, Weiss[33] indicates effect modification so extreme that not only are the combined rate ratios less than multiplicative, but they are also less than additive.

A review of the data has not indicated any easy resolution to the contradictory findings. There are at least three possibilities. One is that many of the results in these studies are based on such small numbers that the variance of estimates of rate ratios is quite large. Hence, the estimates of rate ratios may be inaccurate, and the contradictory findings may, in fact, not be truly contradictory.

Second, there may be substantial inaccuracies in the estimates of both smoking habits and exposure. Smoking data often do not quantify amount smoked. Former smokers and smokers of pipes and cigars may be treated differently from one study to another. Regarding exposure, there are few good data on dose in most of these studies, a common problem in retrospective studies. Differing doses in studies of the same agent, either in terms of quantity or quality, may account for the contradictory findings.

Finally, there is some suggestion in the data reviewed here that studies using an internal nonexposed or low-exposed referent group may fail to detect effect modification, whereas studies using nonoccupational external comparison populations may find such modification. This may occur because referent groups in the internal comparison are, in fact, at increased risk of lung cancer due to their minimal exposure.

There is no well-established reason to expect a priori that if smoking did modify the effect of one agent in causing lung cancer, it would also modify the effect of another agent in the same way. Thus, it is noteworthy that for all four of the agents discussed here, whenever effect modification was observed, nonsmokers (compared to nonexposed nonsmokers) were shown to have a higher rate ratio than smokers (compared to nonexposed smokers).

It is possible that smokers exposed to an occupational lung carcinogen do not fully "express" the combined risks because of competing causes of death. The rate of lung cancer death among these exposed smokers might be so high that virtually all of these men might die of lung cancer, but do not because they die of other causes of death first. Nonsmokers, who live longer in general, might live long enough to allow more of a lung cancer excess to be seen. The use of rates rather than cumulative risks ordinarily corrects for the problem of competing risks to a large extent, but where there are large excesses, rates will also be affected.

Biologically, some investigators have proposed that smoking stimulates mucus production and more efficient

clearance of potential occupational carcinogens, or that smoking constricts small airways, prohibiting the deposit of other occupational carcinogens.[35] Others have said that increased mucus production may provide a physical barrier, protecting the bronchial epithelium from carcinogens,[20,33] or that the increased mucus may metabolize some carcinogens to noncarciogenic substances.[33] There is some evidence from animal studies to support these views.[36]

The fact that in those studies where effect modification does occur, nonsmokers have higher rate ratios than smokers should not be viewed as implying that smoking "protects" the worker from the risks of occupational exposure. Absolute, rather than relative, lung cancer risk remains generally higher in smokers than nonsmokers.

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