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**PART IV. INVOLUNTARY SMOKING
AND LUNG CANCER**

INVOLUNTARY SMOKING AND LUNG CANCER

Introduction

The social pressure to limit smoking in public places (6) reflects concern for protecting nonsmokers from the annoyances of others' cigarette smoke, as well as concern about the possible adverse health effects of involuntary smoking, or secondhand exposure to others' cigarette smoke.

A recent publication presented the scientific evidence linking involuntary smoke exposure to adverse health effects (44). Children of smoking parents had more bronchitis and pneumonia during the first year of life (17); and acute respiratory disease accounted for a higher number of restricted activity days (1.1 days) and bed disability days (0.8 day) in children whose families smoked than in those whose families did not (3). A reduction in exercise tolerance with exposure to sidestream cigarette smoke has been demonstrated in patients with angina pectoris (1), and a decrease in small airway function of the lung equivalent to that observed in light smokers (1 to 10 cigarettes a day) has been reported in adults who never smoked themselves nor lived with smokers, but who were exposed to cigarette smoking in the workplace (49).

Only recently has attention focused on the possibility that lung cancer may be caused by involuntary inhalation of tobacco smoke. This concern is based upon: (1) the occurrence of similar chemical constituents in sidestream smoke (smoke released from the cigarette between active puffs) and mainstream smoke (smoke actively inhaled); (2) the established dose-response relationship between voluntary cigarette smoking and lung cancer, and the absence of evidence establishing a threshold for effect; and (3) the recent epidemiologic studies that examined lung cancer mortality in nonsmoking spouses of cigarette smokers.

Smoke Constituents

The average person spends most of the time indoors where there may be significant exposure to tobacco smoke generated by others (31). For various reasons, the exposure of nonsmokers is more difficult to quantitate than that of the smoker. The constituents of the particulate and gas (vapor) phases of tobacco smoke have been quantitatively analyzed in several studies (8, 22, 37, 38). As is shown in Table 1, many of the chemical constituents of mainstream smoke are also found in sidestream smoke. Some constituents occur in markedly higher concentrations in sidestream than in mainstream smoke (note SS to MS ratio); however, sidestream smoke is released into the ambient air, resulting in dilution of constituents. The resulting concentration of smoke is dependent upon the amount of

TABLE 1.—Constituents of cigarette smoke.¹ Ratio of sidestream smoke (SS) to mainstream smoke (MS)

A. GAS PHASE	MS	SS/MS		MS	SS/MS
Carbon Dioxide	20-60 mg	8.1	Nitrogen Oxides (NO _x)		
Carbon Monoxide	10-20 mg	2.5	Ammonia	80 µg	73
Methane	1.3 mg	3.1	Hydrogen cyanide	430 µg	0.25
Acetylene	27 µg	0.8	Acetonitrile	120 µg	3.9
Propane Propene	0.5 mg	4.1	Pyridine	32 µg	10
Methylchloride	0.65 mg	2.1	3-Picoline	24 µg	13
Methylfuran	20 µg	3.4	3-Vinylpyridine	23 µg	28
Propionaldehyde	40 µg	2.4	Dimethylnitrosamine	10-65 µg	52
2-Butanone	80-250 µg	2.9	Nitrosopyrrolidine	10-35 µg	27
Acetone	100-600 µg				
B. PARTICULATE PHASE					
	MS	SS/MS		MS	SS/MS
"Tar"	1-40 mg	1.7	Quinoline	1.7 µg	11
Water	1-4 mg	2.4	Methylquinolines	0.7 µg	11
Toluene	108 µg	5.6	Aniline	360 ng	30
Stigmasterol	53 µg	0.8	2-Naphthylamine	2 ng	39
Total Phytosterols	130 µg	0.8	4-Aminobiphenyl	5 ng	31
Phenol	20-150 µg	2.6	Hydrazine	32 ng	3
Catechol	130-280 µg	0.7	N'-Nitrosornicotine	100-500 ng	5
Napthalene	2.8 µg	16	NNK ²	80-220 ng	10
Methylnapthalene	2.2 µg	28	Nicotine	1-2.5 mg	2.7
Pyrene	50-200 µg	3.6			
Benzo(a)pyrene	20-40 µg	3.4			

¹Nonfilter cigarette

²NNK = 4-(N-methyl-N-nitrosamino)-1-(3-pyridyl)-1-butanone (tobacco specific carcinogenic nitrosamine)

SOURCE: U.S. Department of Health, Education, and Welfare (44).

smoke generated, the volume of ambient air, and the type and amount of the ventilation of that space (2, 4, 24, 34, 44). In addition, the chemical composition of smoke changes with the passage of time (24a). Further complicating factors include the continuous low-dose exposure of involuntary smokers contrasted with the intermittent high-dose exposure of the active smoker. Thus, many factors complicate the theoretical extrapolation of machine measurements of smoke constituents to the biologic effects to be expected with exposure of nonsmokers.

The actual absorption of smoke constituents by nonsmokers in smoke-filled spaces has not been completely characterized. A few studies have examined the absorption of carbon monoxide by measuring carboxyhemoglobin levels in exposed nonsmokers (44); however, the absorption of most other constituents has not been studied. Furthermore, the pattern of involuntary inhalation probably differs from that of voluntary inhalation of smoke by the smoker, affecting the pattern and amount of deposition or absorption of

chemical constituents in nonsmokers compared to smokers. Differences in the carcinogenicity of sidestream and mainstream smoke may also exist; sidestream smoke condensate is more tumorigenic per unit weight in mouse skin assays than is mainstream smoke condensate (50).

Some evidence exists that suggests, however, that involuntary exposure to cigarette smoke does result in deposition or absorption of constituents. Involuntary inhalation of cigarette smoke has been shown to produce tracheobronchial epithelial metaplasia and dysplasia in animals (23). The applicability of these data to human exposures is not clear, however, since the levels of smoke exposure used in this animal study were substantially higher than those normally encountered by humans in enclosed spaces where smoking is allowed (38). In a smoke-filled, unventilated, unoccupied room, the concentrations of several smoke constituents, including several volatile gases, total particulate matter, and nicotine, remained constant and were higher than when humans were present. Further, several vapor phase constituents such as nitrogen oxide, acrolein, and aldehydes were observed to decrease continuously over 3 hours when humans were placed in the room, despite fresh sidestream smoke being generated to keep the ambient carbon monoxide level stable (24). The difference in absolute levels and the continuing decrease in constituent concentrations despite the continuing addition of smoke to the environment suggest absorption by humans, although the actual site(s) of deposition has not been determined.

Dose-Response Relationships

Examination of the dose-response relationship for voluntary smokers suggests an increased risk with any level of regular cigarette smoking (43). No threshold level of exposure for the development of lung cancer has been established and, therefore, any level of exposure is of concern. Figure 1 reflects the data that led to the scientific consensus that there is no threshold level. This absence of a clear threshold level of exposure raises the issue of whether the levels of exposure reached through involuntary smoking may also produce an increased risk of lung cancer.

Epidemiologic Studies

The use of epidemiologic techniques to search for an association between involuntary smoke exposure and lung cancer has a number of methodologic difficulties.

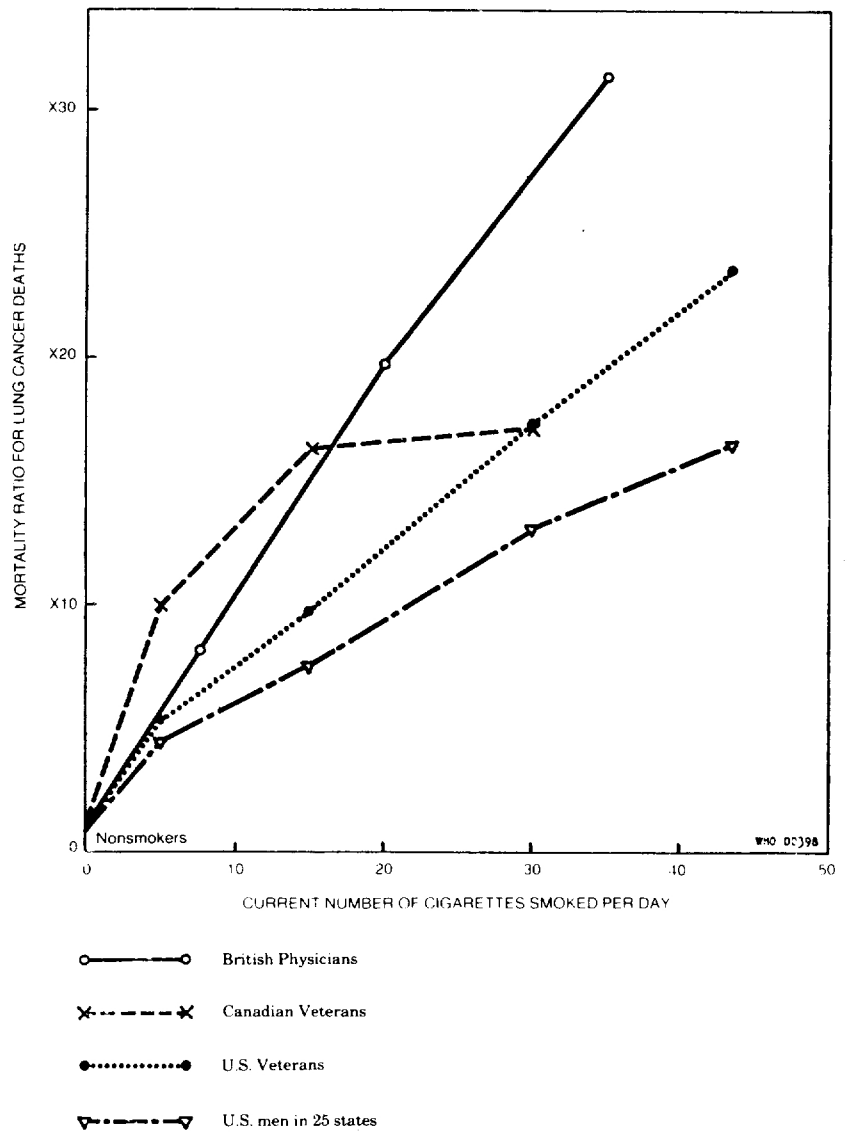


FIGURE 1.—Mortality ratios of deaths from lung cancer in men. Data from four large prospective studies

British Physicians
 Canadian Veterans
 U.S. Veterans
 U.S. men in 25 states

SOURCE: Royal College of Physicians of London (35).

Exposure

An individual's actual smoke exposure dose is difficult to quantify, even for an acute exposure. For the longer exposure periods, as in chronic disease epidemiologic studies, the exposure quantification problems are magnified. Dosage is dependent upon the amount of smoking by those around the nonsmoker, the spatial distance between the nonsmoker and smoker, the duration and frequency of exposure, and a number of other factors that complicate the quantification of involuntary smoke exposure in either retrospective or prospective studies. Several studies have used the smoking habits of the spouse of the nonsmoker as a means of identifying two groups (nonsmokers with smoking or nonsmoking spouses). This estimate of exposure is subject to misclassification, as the nonsmoker may be a former smoker. This may be true for either the nonsmoker being followed or the nonsmoking spouse in the control group. In addition, in societies with a high rate of divorce or multiple marriages, the smoking habits of the current spouse may not approximate the actual exposure. Further, there is a demonstrable correlation between the smoking habits of spouses that decreases the proportion of couples available for study who are discordant for smoking.

Long Latency Periods

Lung cancer follows exposures experienced over decades and, therefore, it is necessary to observe nonsmokers over an extended time in order to estimate their actual exposure.

Other Carcinogenic Exposures

Exposure to cigarette smoke may occur in conjunction with exposure to other occupational or environmental carcinogens. Epidemiologic studies should control for or investigate possible interactions with other environmental exposures as far as possible, but limitations clearly exist here as well. Accurately assessing lifetime exposures and attempting to control for such exposures are difficult, if not impossible.

Current Epidemiologic Evidence

To date, three epidemiologic studies have been published that examine the lung cancer risk of involuntary smoking. Two of these studies (19, 42) were conducted in the relatively traditional societies of Greece and Japan; the third analysis was conducted in the United States by Garfinkel (12), based on data originally collected by Hammond (14).

Trichopoulos et al. used the case-control method of study over the period of September 1978 through June 1980. They identified 51

Caucasian female lung cancer patients and 163 adult female orthopedic patients in Athens. All subjects were questioned on their personal smoking habits, and husbands were classified as nonsmokers (never smoked or quit more than 20 years prior), ex-smokers (stopped smoking 5 to 20 years prior), and current smokers (currently smoking or smoked within 5 years prior to interview). Single women were classified with the group having nonsmoking husbands. The cases and controls did not differ in age, duration of marriage, occupation, education, or place of residence, although specific matching on these characteristics was not performed. Involuntary exposure of the wife was estimated from her husband's daily consumption, from the date of marriage until their divorce, her husband's death, or change in his smoking habits; multiple marriages were also considered.

Excluding 11 voluntary smokers from the 51 female lung cancer cases, and 14 smokers from the 163 controls, the remaining 40 nonsmoking lung cancer patients and 149 nonsmoking control women were compared by their husband's current smoking status, and estimated total cigarettes smoked by the husband by the time of interview. The results are shown in Tables 2 and 3 respectively. Compared with the control group, at interview the lung cancer cases showed 1.8-fold greater probability of being married to an ex-smoker; 2.4-fold greater odds of being married to a light or moderate smoker (20 or fewer cigarettes per day); and 3.4-fold greater odds of being married to a heavy smoker (more than 20 cigarettes per day). The trend observed in these findings was statistically significant, with a p value less than 0.02. Exclusion of single women from this analysis modified the relative risks only slightly. Table 3 shows a similar trend of increasing relative risks in nonsmoking wives with increasing (estimated) total number of cigarettes smoked by the husband prior to the interview.

Some limitations and strengths of this study were recognized and discussed by the authors. Among the limitations were: the number of cases was small; 35 percent of the tumors lacked histologic confirmation; controls were chosen from a different hospital than were the cases; a single unblinded interviewer was used for both cases and controls. On the other hand, the authors suggested that the conservative social setting for this study may be less subject to errors of misclassification resulting from the exposure of nonsmoking wives of nonsmokers to the smoke of others outside the home. The number of cases of adenocarcinoma that were excluded from the analysis is not given. Analysis including such cases would be of interest (16), as many investigators have found cigarette smoking to be a cause of adenocarcinoma of the lung as well as of other histologic types of lung cancer (45). Additional control groups for comparison to the cases might have enhanced the findings of this study.

TABLE 2.—Smoking habits of husbands of nonsmoking women with lung cancer and of nonsmoking control women

Diagnostic group	Nonsmokers	Ex-smokers	Cigarettes per day (current smokers)				Total
			1-10	11-20	21-30	31+	
Lung cancer	11	6	2	13	4	4	40
Controls	71	22	9	32	6	9	149
RR ^a	1.0	1.8	2.4		3.4		
RR ^b	1.0	1.5	2.0		3.0		

^a Relative risk—the ratio of the risk of lung cancer among women whose husbands belong to a particular smoking category to that among women whose husbands are nonsmokers. $X^2=6.45$, $p(2\text{-tail})=0.02$.

^b Analysis excluding single women arbitrarily classified as nonsmokers. $X^2(\text{linear trend})=4.6$, $p<0.03$.

SOURCE: Trichopoulos et al. (42).

TABLE 3.—Distribution of nonsmoking women with lung cancer and of nonsmoking control women according to the estimated total number of cigarettes smoked by their husbands by the time of the interview

Diagnostic group	Total number of cigarettes (in thousands)						Total
	0	1-99	100-199	200-299	300-399	400+	
Lung cancer	8	4	6	9	6	7	40
Controls	56	21	26	16	12	18	149
RR ^a	1.0	1.3	2.5		3.0		

^aRelative risk—the ratio of the risk of lung cancer among women whose husbands belong to a particular smoking category to that among women whose husbands are nonsmokers. $X^2=6.50$, $p(2\text{-tail})<0.02$.

SOURCE: Trichopoulos et al. (1981).

Hirayama (19) used a prospective design in 29 health districts in Japan over 14 years, from 1966 to 1979, in which 91 to 99 percent of the census population was interviewed. He analyzed interview data from 265,118 adults aged 40 years and older, and found that 72.3 percent of the couples had data on the smoking habit of both spouses. Among 91,540 married women, 245 deaths from lung cancer were recorded, of which 174 were nonsmokers. He reported a statistically significant excess rate of lung cancer among nonsmoking wives of smokers as compared to nonsmoking wives of nonsmokers. Table 4 shows the standardized mortality rates for lung cancer in nonsmoking wives, adjusted for age and occupation. There is an apparent dose-response relationship in each of the analyses presented. Certain methodologic details (e.g., the definition of an ex-smoker

husband, the method of age and occupation standardization, and the technique or extent of histologic confirmation) were not presented. Hirayama also examined the effects of voluntary smoking in relationship to involuntary exposure and nonexposure. The standardized annual mortality rate for nonsmokers who were not involuntarily exposed was 8.7 per 100,000. For women who reported being exposed to cigarette smoke only involuntarily, the standardized annual mortality rate was 15.5 per 100,000. For women who voluntarily smoked, the standardized annual mortality rate was 32.8 per 100,000. He concluded that the effect of involuntary smoking was approximately one half to one third that of active or voluntary smoking.

The age and occupation standardized risk ratios in this population failed to show any statistically significant effect of spousal smoking on nonsmoking women's standardized risk ratios for deaths from other causes, including emphysema (although the trend in relative risk was in the same direction as for lung cancer mortality), cervical cancer, stomach cancer, or ischemic heart disease (Table 5); no significant role of spousal alcohol consumption was demonstrated for any of the above diseases.

The public press has reported a possible error in Hirayama's computation of the chi square test of statistical significance (33). However, the scientist to whom this finding was attributed has subsequently stated that he raised questions about the study but denied reaching any conclusion (29a).

Harris and DuMouchel (18) recalculated the chi square using the originally presented data of Hirayama by combining Tables 1 and 2. The calculated chi square of 8.09 yielded a statistically significant two-sided p value of 0.0004.

In a subsequent, more detailed tabular presentation, Hirayama (21a) confirmed the statistically significant excess in lung cancer death rates in wives of smokers when adjusted for husband's age, occupation and smoking habits. In this subsequent analysis, Hirayama restricted his analysis to data from one prefecture for a possible dose-response relationship of involuntary smoking and lung cancer mortality. The exposure of nonsmoking wives was calculated by multiplying the hours of the day the husband was at home by the number of cigarettes smoked per hour, assuming that the number of cigarettes smoked per hour remained constant over waking hours. There was a clear dose-response observed (Table 6) for each of three categories for length of hours and for number of cigarettes smoked per day. The risk of death from lung cancer in nonsmoking women increased with either the time of exposure or increasing daily number of cigarettes. In that set of analyses, the relative mortality risk (as measured by the standardized mortality ratio) observed

TABLE 4.—Standardized mortality for lung cancer in women by age, occupation, and smoking habit of the husband (patient herself a nonsmoker)

Husband's smoking habit	Nonsmoker	Ex-smoker or 1-19/day	≥ 20/day
<i>Husband's age: 40-59 years</i>			
Population of wives	14,020	30,676	20,584
No. of deaths from lung cancer	11	40	36
Occupation-standardized mortality/100,000	5.64	9.34	13.14
<i>Husband's age: ≥ 60 years</i>			
Population of wives	7,875	13,508	4,877
No. of deaths from lung cancer	21	46	20
Occupation-standardized mortality/100,000	15.79	24.44	29.60
Standardized risk ratio for all ages	1.00	1.61	2.08
<i>Husband working in agriculture</i>			
Population of wives	10,406	20,044	9,391
No. of deaths from lung cancer	17	52	24
Age-standardized mortality/100,000	9.54	17.02	18.40
<i>Husband working elsewhere</i>			
Population of wives	11,489	24,140	16,070
No. of deaths from lung cancer	15	34	32
Age-standardized mortality/100,000	9.13	10.46	17.78
Standardized risk ratio for all occupations	1.00	1.43	1.90

SOURCE: Hirayama (19).

among nonsmoking wives of smoking husbands was markedly lower than that observed for women who actively smoked (Figure 2).

The observed differences between wives of smokers and wives of nonsmokers were evident for each of the four socioeconomic status classes.

Hirayama's article has stimulated much discussion, which has been published as Letters to the Editor of the *British Medical Journal* (5, 13, 25a, 27, 27a, 30, 36, 40, 42a). In three replies to the same journal (20, 21, 21a), the reader is referred to the specific issues raised and responded to in these letters.

TABLE 5.—Age-occupation standardized risk ratio for selected causes of death in women by smoking habit of the husband (patient herself a nonsmoker)

Cause of death	Husband's smoking habit			p value *
	Nonsmoker	Ex-smoker, or 1-19/day	≥ 20/day	
Lung cancer (n = 174)	1.00	1.61	2.08	0.0001
Emphysema, asthma (n = 66)	1.00	1.29	1.49	0.474
Cancer of cervix (n = 250)	1.00	1.15	1.14	0.249
Stomach cancer (n = 716)	1.00	1.02	0.99	0.720
Ischaemic heart disease (n = 406)	1.00	0.97	1.03	0.393

* (X² linear trend).

SOURCE: Hirayama (19).

TABLE 6.—How often wives with smoking husbands inhale cigarette smoke passively in Japan (calculation based on a study in Aichi Prefecture, Japan)

No. cigarettes smoked by husband/day	Length of contact in a day					
	1.5 h		4 h		15.0 h	
	Frequency (%)	No. cigarettes to which they were exposed*	Frequency (%)	No. cigarettes to which they were exposed*	Frequency (%)	No. cigarettes to which they were exposed*
1-19 (average 10)	11.8	(0.88)	14.2	(2.55)	6.8	(8.82)
20-29 (average 25)	19.8	(2.21)	25.4	(5.88)	8.6	(22.06)
30-60 (average 45)	5.6	(3.97)	5.2	(10.59)	2.6	(39.71)

*Length of contact multiplied by number smoked in an hour (number smoked in an hour equals average number of cigarettes smoked in a day divided by total hours awake).

SOURCE: Hirayama (27).

Nonetheless, the applicability of such results to the U.S. population remains to be established.

Garfinkel (12) published an analysis of data from the American Cancer Society's prospective study conducted from 1960 through 1972. He reported results on 176,739 nonsmoking women who were then married (a) to men who never smoked, (b) to men who currently smoked less than 20 cigarettes per day, or (c) to men who currently smoked 20 or more cigarettes per day. In an analysis that did not attempt to control for possible confounding variables, the observed to expected lung cancer mortality ratio (expected numbers were derived from the lung cancer rates of women married to nonsmokers by 5-year age groups) was 1.27 for women married to smokers of less than 20 cigarettes per day and 1.10 for women married to smokers of 20 or more cigarettes per day. These increases in mortality ratios over those of wives of nonsmokers were reported to be not statistical-

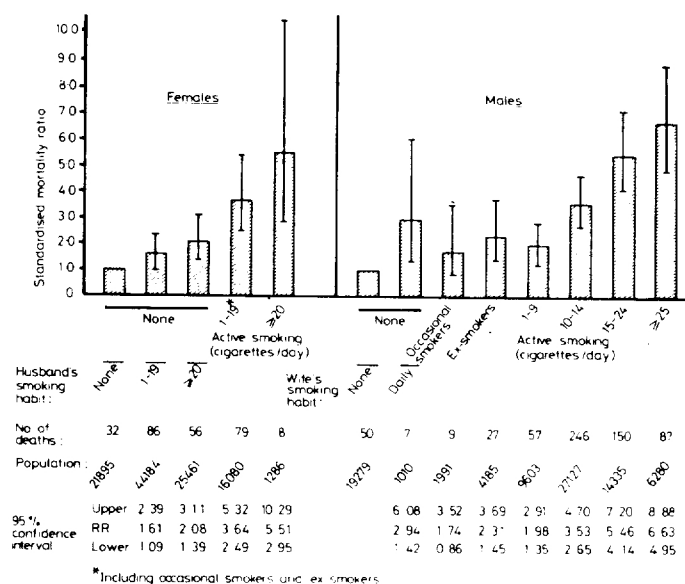


FIGURE 2.—Active and passive smoking and standardised mortality rates for lung cancer: relative risks (RR) with 95 percent confidence intervals—prospective study, 1966–1979, Japan

*Includes occasional smokers and ex-smokers
SOURCE: Hirayama (21a).

TABLE 7.—Observed versus expected* lung cancer deaths among nonsmoking women with cigarette-smoking husbands, ACS study, 1960–1972**

Parameter	Husband did not smoke	Husband smoked < 20 cigarettes per day	Husband smoked ≥ 20 cigarettes per day
Observed deaths	65	39	49
Expected deaths	65.00	30.67	44.67
Mortality ratio	1.00	1.27	1.10

*Expected deaths are based on the lung cancer rates by 5-year age groups in women with nonsmoking husbands applied to the person-years of women with smoking husbands.

**The 95 percent confidence limits for women with husbands smoking < 20 cigarettes/day were 0.85 and 1.89; for women with husbands smoking ≥ 20 cigarettes/day, they were 0.77 and 1.61.

SOURCE: Garfinkel (12).

ly significant (p value not specified) (Table 7), and no dose-response effect was evident.

The same three groups of nonsmoking women were compared in another analysis. In an attempt to eliminate possible confounding

TABLE 8.—Matched group study: Adjusted lung cancer deaths among women with nonsmoking husbands matched* with women with smoking husbands

Group	Number of adjusted lung cancer deaths	Ratio	p ^a
Nonsmoking husband	25.6	1.00	
Husband smoked < 20 cigarettes/day	35.0	1.37	NS
Nonsmoking husband	34.5	1.00	
Husband smoked ≥ 20 cigarettes/day	35.8	1.04	NS

*Matched on the basis of (a) wife's 5-year age group, (b) husband's occupational exposure, (c) highest educational level of husband or wife, (d) race, (e) urban-rural residence, and (f) absence of serious disease at the start of the study.

^aNS = not significant.

SOURCE: Garfinkel (12).

variables, pairs of women were matched on multiple factors. The number of deaths in each matched diad was "adjusted" as described in a prior publication (15). The results of this analysis are shown in Table 8. Neither group of nonsmoking wives of smokers showed a statistically significant difference ($p > 0.05$); there is no dose-response pattern apparent. The actual size and composition of the matched study population, however, were not shown. The author concluded that any effect passive smoking had on lung cancer mortality would be small.

The author presented the limitations of this analysis. The study was not designed to examine the question of effects of passive smoking and, therefore, there were difficulties with the accurate assessment of exposure. The appropriateness of this analysis of the ACS data has been questioned (16) for this reason. The difficulties include the measurement of involuntary exposure to smoke from persons other than the husband, and an inability to adjust for changes in husband's smoking subsequent to actual interview or for exposure(s) from previous husbands. A study should be specifically designed to measure exposure, as neither the Japanese (19) nor the ACS study met that criterion. Additionally, among 564 cases of lung cancer in nonsmoking women, the husband's smoking status was available for only 153 (27 percent).

Thus, each of the three epidemiologic studies published to date shows an increased risk of lung cancer with involuntary smoke exposure (Table 9). The results were statistically significant in two of the three studies, which also found a dose-response effect. The evidence currently available suggests that involuntary smoke exposure may increase the risk of lung cancer in nonsmokers, but