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Involuntary smoking and lung cancer

by Paolo Boffetta, MD[1]

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Involuntary smoking contains human carcinogens. Exposure prevalence among adults is on the order of 40%. A meta-analysis of epidemiologic studies on lung cancer and exposure to involuntary smoking from the spouse included 51 studies. The overall relative risk (RR), based on 7369 cases of lung cancer, was 1.25 [95% confidence interval (95% CI) 1.15–1.37]. No evidence existed of an RR difference between the two genders, and study design had no influence on the results. The summary RR was lower for adenocarcinoma than for other histological types. In the largest studies cumulative exposure suggested a dose-response relationship with a unit risk of similar magnitude. The summary RR was 1.17 (95% CI 1.04–1.32) for workplace exposure. Several sources of bias may lead to both overestimation and underestimation of true association, and the most plausible interpretation favors a causal association. Even if excess risk from exposure to involuntary smoking is small, its large prevalence makes it an important environmental carcinogen.

Key terms environmental tobacco smoke, meta-analysis, passive smoke.

Over the last 20 years, a large body of evidence has accumulated showing a carcinogenic effect for involuntary smoking on the human lung. Regulatory authorities have considered the evidence strong enough to justify the classification of involuntary smoking as a human carcinogen (1). In parallel, an extensive amount of literature has been published on the interpretation of the results of epidemiologic studies on the health effects of involuntary smoking (2). Criticisms were raised largely to serve the interests of the tobacco industry (3). However, the extraordinary attention that the interpretation of studies on involuntary smoking and lung cancer has received may contribute to the advancement of the methodology of research on weak carcinogens in general.

In this paper the accumulated evidence of a carcinogenic effect of adult exposure to involuntary smoking on the human lung is reviewed, mainly from epidemiologic studies. In addition, the critical methodological problems related to the interpretation of epidemiologic studies are discussed with respect to exposure to involuntary smoking and the risk of lung cancer. Other possible health effects of involuntary smoking have been the subject of reviews and meta-analyses [neoplasms other than those of the lung (4), adult cancer from childhood exposure (5), childhood neoplasms (5), cardiovascular diseases (6), nonneoplastic respiratory diseases in children and adults (7), and reproductive toxicity (8)], and they are reviewed elsewhere in this issue of the *Scandinavian Journal of Work, Environment & Health*.

IARC has not formally evaluated involuntary smoking within its monograph program. Two evaluations of the carcinogenicity of tobacco smoking, however, contain the statement that involuntary smoking gives rise to a risk of lung cancer (9, 10). A formal evaluation of the available evidence is scheduled to take place in 2002 (see http://monographs.iarc.fr).

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Characteristics and exposure circumstances of involuntary smoking

Carcinogens in involuntary smoking

Involuntary smoking consists of exposure to a complex mixture of chemicals generated during the burning of tobacco products. It contains sidestream smoke — the material emitted from the smoldering tobacco product between puffs — as well as exhaled mainstream smoke, mainstream smoke emitted at the mouthpiece during puff drawing, and compounds diffused through the wrapper.

At least half of the smoke generated by a smoking cigarette is sidestream smoke emitted from the smoldering cigarette. Out of the very large number of compounds identified in tobacco smoke, approximately 400 have been measured quantitatively in both mainstream and sidestream smoke (11). The composition of sidestream smoke varies depending on the chemical composition of the tobacco, the design of the tobacco product, and the circumstances of smoking (12).

Once emitted into the air, sidestream smoke — as well as various components of mainstream smoke — can undergo dilution, chemical reactions, deposition, and other removal processes. This dilution results in a decrease in the concentration of the airborne constituents, in the alteration of the size distribution of suspended particles, and in the chemical modification of the constituents.

Nicotine, which is the principal alkaloid in tobacco, is a major contributor to the addictive properties of tobacco (11). Nicotine exerts a range of pharmacological and toxicologic actions and may be directly responsible for some of the adverse health effects associated with smoking, including involuntary smoking. Carbon monoxide is likely to contribute to the effect on the cardiovascular system.

Compounds identified in tobacco smoke include recognized human carcinogens such as 4-aminobiphenyl and arsenic, probable human carcinogens such as benzo(a)pyrene and other polycyclic aromatic hydrocarbons (PAH), as well as 1,3-butadiene. Tobacco smoke also contains possible human carcinogens, including PAH, N-nitrosamines (eg, N'-nitrosonornicotine), and other nitrosocompounds (9). The inhalation of nitrogen oxides and amines in tobacco smoke may also contribute to the endogenous formation of carcinogenic N-nitrosamines (13).

In addition, tobacco and its smoke contain heavy metals known to be carcinogenic, such as arsenic, cadmium, and chromium, which are derived either from soil or from anthropogenic sources. Finally, tobacco contains several naturally occurring radionuclides, of which the most important is the alpha-emitter polonium-210 (14).

Measurements of exposure to involuntary smoking

Given the spatial and temporal variation of the concentration of constituents of involuntary smoking in indoor and outdoor environments, it is not feasible to determine accurately the long-term exposure history of a person. One option to circumvent this difficulty is to classify the subjects into categorical groups of exposure (eg, none, low, medium, or high). This approach makes the best use of the limited exposure information available, without compromising the validity of the study results; however, it decreases the power of the study and therefore possibly results in false negative results. This problem is particularly relevant in the case of studies of lung cancer, a disease that requires a latency of 10 or more years from the biologically relevant exposure.

Methods for assessing exposure to involuntary smoking have been reviewed by the California Environmental Protection Agency (11). In studies of lung cancer, involuntary smoking is usually assessed via questionnaires that reconstruct the characteristics, patterns, and extent of past exposure. Other methods for assessing exposure include measurements of concentrations of relevant chemicals (eg, respirable suspended particulates, nicotine, N-nitrosamines, PAH) in indoor air, use of personal monitors, and the measurement of biomarkers of exposure. These methods, in particular measurement of involuntary smoke constituents and their metabolites (nicotine, cotinine, carbon monoxide, carboxyhemoglobin, thiocyanates, as well as tobacco-specific nitrosamines and their metabolites) in tissues and body fluids, may be superior to the use of questionnaires on recent exposure. However, in order for past exposure to be assessed, they require that measures or biological samples be collected at the relevant time and properly stored. A compromise between the validity, the precision, and the time relevance of the measurement can be offered by biomarkers of medium-term exposure (ie, up to several months), such as hair nicotine levels (15). Such medium-term biomarkers still need to be fully validated, however.

Studies on involuntary smoking comparing exposed and unexposed nonsmokers, as well as active smokers (16–22) have consistently found that measurements of cotinine in the urine, saliva, or serum can distinguish active smokers from unexposed and exposed nonsmokers. Findings have been less consistent with regard to the use of such assays to distinguish between self-reported unexposed and exposed nonsmokers. Potential reasons for this inconsistency include intersubject variability in nicotine metabolism, time of day of sample collection, misreporting of smoking status, misreporting of nonsmoking status, adjustment of cigarette consumption for nicotine content, and over- or underreporting of exposure to involuntary smoking (22).

Exposure prevalence

Information on the prevalence of exposure to involuntary smoking and its determinants is available from a large number of studies. These studies have been reviewed by the California Environmental Protection Agency (11). Table 1 reports the results of some of the largest available studies. The exposure prevalence among nonsmoking adults in the United States is on the order of 40%, and the workplace represents the main source of exposure. Young adults report a higher prevalence of exposure than older persons; some evidence suggests a higher exposure among Blacks and persons with a lower educational level. No consistent differences appear between genders. Few data are available from Europe. The prevalence among referents included in a multicenter case-referent study was 78%. Also in this study, there was an inverse relationship between age and the prevalence of exposure.

Epidemiologic evidence of increased lung cancer risk

Since 1981, several epidemiologic studies have been published on the association between exposure to involuntary smoking and lung cancer. Reviews and meta-analyses have been published, in particular in recent years (28–31). The two sources of adult exposure to involuntary smoking that have been more frequently studied are the spouse and the workplace. Additional sources include public settings (eg, bars and restaurants), public transport, and other social occasions. In several studies, the definition of spousal smoking has been expanded to include other cohabitants (eg, parents living in the home of the adult subject).

This review concentrates on adult exposure from the spouse (and other cohabitants) and at the workplace. These types of exposure have been found to represent the main sources of exposure (32). Relevant studies have been identified through a search of the medical literature and automatic databases such as Medline, previous reviews, and lists of references of relevant studies. The most recent date of publication was December 2000. When multiple articles reported results based on the same subjects (either as a subset of a larger study or as an update of a previous investigation), only the most extensive or recent analysis has been retained. The very first two papers on the association between spousal involuntary smoking and lung cancer (33, 34) have therefore been excluded, since they were updated a few years later. Among other studies that have been excluded are those by Nyberg et al (35) and Kreuzer et al (36), which include material published elsewhere (37, 38). Reports that did not provide sufficient detail either to judge the quality of the study or to abstract the risk estimate have also been excluded.

From each study the following components have been abstracted: information on the study area and study design, the definition of exposure, and the gender-specific risk estimates [in most cases odds ratios or rate ratios, defined here as relative risks (RR)]. In a few cases the relative risk has been calculated from the raw data (eg, number of exposed and unexposed cases and referents). Histology-specific results were also abstracted, as well as results on the duration of exposure to involuntary smoking from the spouse (the quantitative variable of exposure for which the largest number of results was available). Since the categories of duration of exposure were heterogeneous among the studies, each category was classified according to the midpoint (eg, 1–20 years was classified as 10 years; 5 years were added to open categories so that 30 or more years was classified as 35 years) and grouped risk estimates according to three broad midpoint groups (1–14, 15–29, and ≥30 years).

The meta-analysis was based on random-effects models (39). Publication bias was assessed using the

Table 1. Results of selected studies on the prevalence of current exposure to involuntary smoking among adults. (US=United States)

Study	Location	Year	N	Exposure	Prevalence (%)	Comments
Friedman et al, 1983 (23)	San Francisco, US	1979–1980	37 881	Any	63	Inverse relation with age
Coultas et al, 1987 (24)	New Mexico, US	1984–1985	1 360	Any [a]	39	Workplace major source of exposure for adults
Jenkins, 1992 (25)	California, US	1987–1988	1 579	Any	43	Workplace major source of exposure for adults
Borland et al, 1992 (26)	California, US	1990	7 301	Workplace	31	Inverse relation with age and education
Pirkle et al, 1996 (27)	United States	1988–1991	14 269	Any	37	Higher prevalence among Blacks and men
Boffetta et al, 1998 (37); Boffetta et al, 1998 (38)	7 European countries	1988–1994	1 540	Any [b]	78	Inverse relation with age

[a] Based on cotinine measurements.
[b] Lifetime exposure.

graphic test proposed by Egger et al (40). For the data analysis the statistical package STATA has been used.

Table 2 reports the results of the individual case-referent studies that were retained for the meta-analysis, and table 3 reports similar results for cohort studies. Altogether 51 studies were identified, providing 59 gender-specific risk estimates. The results specific for histology and the duration of exposure of individual studies are available upon request.

The results of the meta-analysis on ever exposure to involuntary smoking from the spouse are reported in table 4. There was evidence of heterogeneity in the results, which can be explained mainly by differences among the results of studies conducted in different geographic regions. The overall relative risk, based on 7369 cases of lung cancer, was 1.25, with a 95% confidence interval (95% CI) of 1.15–1.37. Most of the cases included in the studies were women. There was no evidence of a difference in relative risk between the two genders, although the summary risk estimate for the men did not reach the 5% level of statistical significance because of the relatively small number of cases. Most of the available studies were of the case-referent design, and the summary relative risk of studies based on hospital series of cases and referents was higher than that of population-based studies. The results of cohort studies approached those of hospital-based case-referent studies. The studies from China (including Hong Kong and Taiwan) and those from the United States each contributed more than one-third of the total cases, and they yielded a lower summary risk estimate than the studies conducted in Europe and elsewhere (mainly Japan and other Asian countries). It is worth noting that, with the partial exception of China (P-value 0.1), the heterogeneity of the results within each geographic region was small. There was a suggestion of a smaller excess in studies published after 1993 as compared with that of previous studies. The results according to histological type (this information was available for 59% of the cases) showed a lower summary relative risk for adenocarcinoma than for other histological types, with no clear difference (based on relatively small numbers) between squamous- and small-cell carcinoma. The meta-analysis on duration of exposure was based on results from 13 studies. The results, which are shown in figure 1, provide no evidence of a dose-response relationship. However, some of the largest studies presented results based on various indicators of cumulative exposure to involuntary smoking. Figure 2 presents the results oftwo large multicenter studies according to cumulative exposure (pack-years of tobacco smoked by the spouse), which suggest a dose-response relationship with a unit risk of similar magnitude.

There was evidence of publication bias (P-value 0.005); positive studies were more likely to be published than negative ones. However, the restriction of the meta-analysis to large studies, among which there was no evidence of publication bias, largely confirmed the results reported in table 4. For example, a meta-analysis of the 15 risk estimates, based on more than 150 cases (providing 63% of all available cases), resulted in a summary relative risk of 1.22 (95% CI 1.05–1.42), with a P-value of the test for publication bias of 0.08. As shown in table 4, publication bias seems to have affected mainly Chinese studies and studies published between 1987 and 1993.

A total of four studies provided relative risks for exposure among women to involuntary smoking from cigars and pipes (84–87). All the relative risks were above unity; the meta-relative risk was 1.17 (95% CI 0.99–1.38, P-value of test for publication bias 0.4).

The results of the individual studies on the risk of lung cancer from workplace exposure to involuntary smoking are reported in table 5. There were 20 gender-specific risk estimates from 16 studies. The results of the meta-analysis are reported in table 6. The summary relative risk was 1.17 (95% CI 1.04–1.32), without heterogeneity among the genders. There was no evidence of heterogeneity or publication bias among the studies.

The results on duration of exposure to involuntary smoking at the workplace are few. A dose-response relationship, however, was suggested in a multicenter case-referent study from the United States (85), but not in a similar study from Europe (37, 38).

Evidence from molecular epidemiologic studies

In recent years, studies on the mechanisms of carcinogenesis have provided information on the interaction between constituents of involuntary smoking and relevant biological targets. They include studies of protein and DNA (deoxyribonucleic acid) adducts, used as markers of exposure or biochemical effect (88, 89). Although the data on adducts are limited, they suggest that components of involuntary smoking interact with relevant biological targets in a manner similar to that of compounds of active smoking. Results of studies of p53 mutations in cases of lung cancer among nonsmokers are compatible with a mechanism of the carcinogenesis of involuntary smoking similar to that of active smoking (90–92). A few studies of genetic polymorphism of genes encoding for enzymes involved in the metabolism of tobacco carcinogens, such as glutathione-S-transferase M1 and N-acetyl-transferase 2 have so far provided conflicting results (93–95). Mechanistic studies of involuntary smoking and lung cancer are reviewed in detail elsewhere in this issue (96). They have the potential to provide important additional information on the carcinogenic effect of involuntary smoking.

Table 2. Case-referent studies of lung cancer and exposure to smoke of the spouse. (RR = relative risk, 95% CI = 95% confidence interval)

Study [a]	Country	Design	Additional information	Gender	Cases (N)	Referents (N)	RR	95% CI
Chan & Fung, 1982 (41)	Hong Kong	Hospital-based study	·	Women	84	139	0.75	0.43– 1.30
Correa et al, 1983 (42)	United States	Hospital-based study	·	Women	22	133	2.07	0.82– 5.20
				Men	8	180	2.0	0.4 –10
Trichopoulos et al, 1983 (43)	Greece	Hospital-based study	·	Women	77	225	2.1	1.2 – 3.6
Buffler et al, 1984 (44)	United States	Population-based study	Results by duration of exposure	Women	41	196	0.78	0.34– 1.81
				Men	11	90	0.52	0.14– 1.74
Kabat & Wynder, 1984 (45)	United States	Hospital-based study	·	Women	53	53	0.9	0.4 – 2.1
				Men	25	25	1.3	0.3 – 4.9
Lam, 1985 (46)	Hong Kong	Population-based study	·	Women	60	144	2.01	1.09– 3.72
Garfinkel et al, 1985 (84)	United States	Hospital-based study	Results by histology	Women	134	402	1.22	0.97– 1.71
Wu et al, 1985 (47)	United States	Population-based study	Results by histology	Women	29	62	1.2	0.5 – 3.3
Akiba et al, 1986 (102)	Japan	Population-based study	Results by duration of exposure	Women	94	270	1.5	1.0 – 2.5
				Men	19	110	1.8	0.5 – 5.6
Lee et al, 1986 (48)	United Kingdom	Hospital-based study	·	Women	32	66	1.0	0.37– 2.71
				Men	15	30	1.3	0.38– 4.39
Koo et al, 1987 (49)	Hong Kong	Population-based study	Results by duration of exposure	Women	88	137	1.64	0.87– 3.09
Pershagen et al, 1987 (50)	Sweden	Population-based study	Results by histology	Women	67	347	1.2	0.7 – 2.1
Humble et al, 1987 (51)	United States	Population-based study	Results by duration of exposure	Women	20	162	2.6	1.2 – 5.6
Lam et al, 1987 (52)	Hong Kong	Hospital-based study	Results by histology	Women	199	335	1.65	1.16– 2.35
Gao et al, 1987 (53)	China	Hospital-based study	·	Women	246	375	0.9	0.6 – 1.4
Brownson et al, 1987 (54)	United States	Population-based study	Results by histology	Women	19	47	1.68	0.39– 2.97
Geng et al, 1988 (55)	China	Hospital-based study	·	Women	54	93	2.16	1.08– 4.29
Shimizu et al, 1988 (56)	Japan	Hospital-based study	·	Women	90	163	1.08	0.64– 1.82
Inoue & Hirayama, 1988 (57)	Japan	Hospital-based study	·	Women	22	47	2.55	0.74– 8.78
Svensson et al, 1989 (58)	Greece	Population-based study	·	Women	34	174	1.26	0.57– 2.81
Janerich et al, 1990 (59)	United States	Population-based study	Results by duration of exposure	Both genders	129	129	0.93	0.55– 1.57
Kalandidi et al, 1990 (60)	Greece	Hospital-based study	Results by histology	Women	91	120	2.11	1.09– 4.08
Sobue, 1990 (61)	Japan	Hospital-based study	·	Women	144	731	1.13	0.78– 1.63
Wu-Williams et al, 1990 (62)	China	Population-based study	·	Women	417	602	0.7	0.6 – 0.9
Liu et al, 1991 (63)	China	Population-based study	·	Women	54	202	0.77	0.30– 1.96
Brownson et al, 1992 (64)	United States	Population-based study	·	Women	431	1166	1.1	0.8 – 1.3
Stockwell et al, 1992 (65)	United States	Population-based study	Results by duration of exposure and histology	Women	210	301	1.6	0.8 – 3.0
Liu et al, 1993 (66)	China	Hospital-based study	·	Women	38	69	1.7	0.7 – 3.8
Fontham et al, 1994 (85)	United States	Population-based study	Results by duration of exposure and histology	Women	651	1253	1.29	1.04– 1.60
Kabat et al, 1995 (67)	United States	Hospital-based study	·	Women	69	187	0.95	0.53– 1.67
				Men	41	117	1.13	0.53– 2.45
Sun et al, 1996 (68)	China	Hospital-based study	·	Women	230	230	1.16	0.80– 1.69
Wang et al, 1996 (69)	China	Population-based study	·	Women	135	135	1.11	0.65– 1.88
Ko et al, 1997 (70)	Taiwan	Hospital-based study	·	Women	105	105	1.3	0.7 – 2.5
Zaridze et al, 1998 (71)	Russia	Hospital-based study	Results by histology	Women	189	358	1.53	1.06– 2.21
Boffetta et al, 1998 (37, 38)	Europe	Hospital-based study [b]	Results by duration of exposure and histology	Women	509	1011	1.09	0.85– 1.40
				Men	141	550	1.55	0.82– 2.94
Shen et al., 1998 (72)	China	Population-based study	·	Women	70	70	1.63	0.68– 3.89
Boffetta et al, 1999 (73)	Europe	Hospital-based study	Results by histology	Women	70	178	1.0	0.5 – 1.8
Zhong et al, 1999 (74)	China	Population-based study	Results by duration of exposure and histology	Women	504	601	1.1	0.8 – 1.5
Rapiti et al, 1999 (75)	India	Hospital-based study	Results by histology	Both genders	58	123	1.1	0.5 – 2.6
Wang et al, 2000 (76)	China	Population-based study	·	Women	200	407	1.03	0.6 – 1.7
			·	Men	33	114	0.56	0.2 – 1.4
Lee et al, 2000 (77)	Taiwan	Hospital-based study	·	Women	268	445	2.2	1.5 – 3.3
Zhou et al, 2000 (78)	China	Population-based study	Results by duration of exposure and histology	Women	72	72	0.94	0.45– 1.97

[a] When results based on the same subjects (either as a subset of a larger study or as an update of a previous investigation) were available from different articles, only the most extensive or recent analysis is reported.

[b] The study by Boffetta et al (37, 38) has a mixed hospital- and population-based design.

Table 3. Cohort studies of lung cancer and exposure to smoke of the spouse. (RR = relative risk, 95% CI = 95% confidence interval)

Study [a]	Country	Additional information	Gender	Cases (N)	RR	95% CI
Garfinkel, 1981 (79)	United States	·	Women	153	1.17	0.94– 1.44
Hirayama, 1984 (80)	Japan	·	Women	200	1.45	1.02– 2.08
			Men	64	2.25	1.06– 4.76
Butler, 1988 (81)	United States	·	Women	8	2.02	0.48– 8.56
Hole et al, 1989 (82)	United Kingdom	·	Women	6	2.41	0.45–12.8
Cardenas et al, 1997 (86)	United States	Results by duration of exposure	Women	150	1.2	0.8 – 1.6
			Men	97	1.1	0.6 – 1.8
Jee et al, 1999 (83)	Korea	Results by duration of exposure	Women	79	1.9	1.0 – 3.5

[a] When results based on the same subjects (either as a subset of a larger study or as an update of a previous investigation) were available from different articles, only the most extensive or recent analysis have been reported.

Table 4. Meta-analysis of ever exposure to passive smoke from the spouse. (RR = relative risk, 95% CI = 95% confidence interval)

Characteristic	Risk estimate (N)	Cases (N)	Heterogeneity	Publication bias	RR	95% CI
Overall	59	7369	0.005	0.003	1.25	1.15–1.37
Gender						
Male	9	454	0.5	0.9	1.25	0.95–1.65
Female	45	6708	0.002	0.07	1.25	1.14–1.38
Both genders	3	207	0.09	0.5	1.34	0.72–2.49
Study design						
Hospital case-referent study	27	3014	0.2	0.2	1.31	1.16–1.47
Population case-referent study	24	3598	0.007	0.1	1.17	1.00–1.36
Cohort study	8	757	0.5	0.05	1.29	1.12–1.49
Region						
China	18	2857	0.1	0.002	1.20	0.97–1.48
United States	21	2511	0.8	0.9	1.20	1.09–1.32
Europe	11	1231	0.5	0.05	1.32	1.13–1.54
Other	9	770	0.6	0.3	1.40	1.17–1.67
Year of publication						
1981–1986	18	1121	0.4	0.1	1.30	1.13–1.49
1987–1993	21	2577	0.001	0.001	1.30	1.08–1.57
1994–	20	3671	0.4	0.9	1.24	1.12–1.36
Histology						
Adenocarcinoma	13	2159	0.6	0.4	1.28	1.13–1.44
Nonadenocarcinoma	12 [a]	2171	0.3	0.2	1.43	1.14–1.79
Squamous-cell carcinoma	5	721	0.1	0.4	1.38	0.87–2.20
Small-cell carcinoma	2	340	0.4	NA	1.47	0.84–2.56

[a] Five risk estimates refer to cases other than adenocarcinoma without further specification.

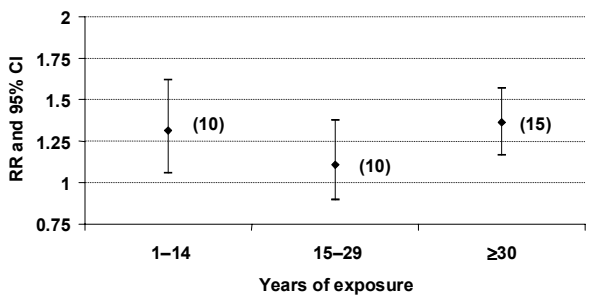

Figure 1. Summary relative risk of lung cancer by duration of exposure to passive smoke from the spouse. Number of risk estimates in parentheses.

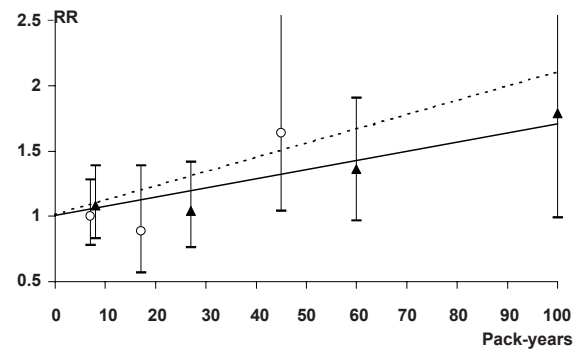

Figure 2. Relative risk of lung cancer by cumulative exposure to involuntary smoking. [Circles: Boffetta et al, 1998 (37), triangles: Fontham et al, 1994 (85)]

Table 5. Relative risk (odds ratios) of lung cancer from workplace exposure to passive smoke. (RR=relative risk, 95% CI=95% confidence interval)

Study [a]	Gender	RR	95% CI
Kabat & Wynder, 1984 (45)	Women Men	0.7 3.3	0.3 – 1.5 1.0 –10.5
Garfinkel et al, 1985 (84)	Women	0.93	0.73– 1.18
Wu et al, 1985 (47)	Women	1.3	0.5 – 3.3
Lee et al, 1986 (48)	Women Men	0.63 1.61	0.17– 2.33 0.39– 6.60
Koo et al, 1987 (49)	Women	1.64	0.87– 3.09
Kalandidi et al, 1990 (60)	Women	2.2	0.8 – 5.7
Fontham et al., 1994 (85)	Women	1.39	1.11– 1.74
Kabat et al, 1995 (67)	Women Men	1.15 1.02	0.62– 2.13 0.50– 2.09
Wang et al, 1996 (69)	Women	0.89	0.45– 1.77
Ko et al, 1997 (70)	Women	1.1	0.4 – 3.0
Zaridze et al, 1998 (71)	Women	0.88	0.55– 1.41
Boffetta et al, 1998 (37, 38)	Women Men	1.17 0.99	0.91– 1.51 0.58– 1.68
Boffetta et al, 1999 (73)	Women	1.2	0.6 – 2.5
Zhong et al, 1999 (74)	Women	1.7	1.3 – 2.3
Rapiti et al, 1999 (75)	Both genders	1.1	0.3 – 4.1
Lee et al, 2000 (77)	Women	1.2	0.5 – 2.4

[a] See table 3 for details on the study design.

Table 6. Meta-analysis of ever exposure to passive smoke at the workplace. (RR = relative risk, 95% CI = 95% confidence interval)

Characteristic	Risk estimate (N)	Cases (N)	Hetero-geneity	Publi-cation bias	RR	95% CI
Overall	20	3248	0.3	0.7	1.17	1.04–0.32
Gender						
Men	4	153	0.3	0.2	1.23	0.78–1.94
Women	15	3037	0.2	0.7	1.17	1.02–1.33

Discussion

As in previous meta-analyses, the summary estimate of this study for the excess risk of lung cancer from exposure to involuntary smoking from the spouse resulted in an excess risk on the order of 25% (28, 31). The excess risk from exposure at the workplace was of similar magnitude. While no dose-response was apparent in the analysis by duration of exposure, the largest and most informative studies reported a positive relationship with estimated cumulative exposure. Other features of the analysis were the presence of an excess from exposure to involuntary smoking from cigars and pipes and a higher risk for squamous- and small-cell carcinoma than for adenocarcinoma.

The analysis of publication bias suggested a possible lack of small studies that show no effect of involuntary smoking. However, as the tests for publication bias, including the one used in this study, have not yet been fully characterized from a statistical viewpoint, care should be taken in interpreting their results.

The data on the risk of lung cancer following exposure to involuntary smoking represent a very large body of evidence as compared with those available for other environmental contaminants. A causal association between exposure to involuntary smoking and lung cancer is now accepted in the scientific community (2) and by regulatory agencies (1), on the basis of the consistency of the association and the evidence of a dose-response relationship. However, some criticism has been raised against this conclusion. It is summarized in table 7, together with the responses that have been provided. (For a detailed discussion, see reference 28.)

The criticism may contain some truth, in particular with respect to the early epidemiologic studies, which were conducted according to a methodology that, today, would not be considered fully adequate. However, it is unlikely that the resulting bias would have systematically affected studies conducted in different locations and time periods and with different methodologies. The fact that a small increase in risk has been confirmed in recent large studies which addressed most of the criticisms

Table 7. Major criticism of a causal interpretation of evidence of an association between exposure to involuntary smoking and lung cancer.

Criticism	Responses
Misclassification of former and current smokers as nonsmokers [Lee & Forey, 1996 (97)]	- Biomarker-based studies suggest misclassification to be small — Wells et al, 1998 (29) - Multiple reports of smoking and use of surrogate information suggest limited misclassification — Nyberg et al, 1997(98)
Reporting bias (ie, cases more likely to report exposure than referents)	- Cohort studies not subject to this bias - Hospital referents more similar to lung cancer cases than population referents, yet comparable risk estimate - Lack of consistent evidence of an effect of childhood exposure — Boffetta et al, 2000 (5)
Confounding by other risk factors of lung cancer	- Most occasional smokers have very low consumption — Nyberg et al, 1998 (99) - No evidence of confounding by diet or occupation — Hackshaw et al, 1997 (28)
Incompatibility with extrapolation from the results of studies on active smoking	- Extrapolations from active smoking studies questionable — National Research Council, 1986 (100) - Multistage models fit risk estimates in the range of exposure experienced by nonsmokers — Puntoni et al, 1995 (101)
Lack of dose-response in many studies	- Quantitative assessment of involuntary smoking exposure subject to misclassificatin

listed in table 7 is a further argument in favor of a causal interpretation of the evidence.

Furthermore, there are reasons why the association estimated from the epidemiologic studies may actually represent an underestimate of the true risk and therefore balance off the possible effect of the biases listed in table 7.

It is plausible that the questionnaires used and the data obtained do not truly describe the biologically relevant exposure to involuntary smoking and lead to nondifferential misclassification of exposure. Further misclassification of the involuntary smoking exposure (defined by multiple sources, duration, intensity, and time since exposure), which results from summarizing the available data into relatively simple exposure variables, may also explain some of the variation in the results between different studies and for different variables. Misclassification can also be exacerbated by the important role of workplace exposure shown in exposure assessment studies (32). Finally, the timing of exposure, in particular time since quitting exposure, is a potentially important aspect of the association. A few studies have analyzed lung cancer risk and time since last exposure to involuntary smoking (37, 38, 43, 102, 103), and the results suggest that current exposure (ie, continuing into the most recent 10- to 20-year period for a person) may be important for the risk of lung cancer. This possibility is consistent with the decreased excess risk demonstrated among smokers after they quit smoking (104). Similarly, the lack of consistent evidence for an increased risk in association with involuntary smoking exposure during childhood (5) suggests that distant exposures may be less important.

Furthermore, the epidemiologic studies compare groups at different levels of involuntary smoking exposure with a reference group considered unexposed. However, involuntary smoking exposure is widespread and was even higher in the past, and subjects classified as unexposed are likely to have experienced exposures that are not captured by the questionnaires. Such background exposure would contribute to an underestimation of the relative risk of lung cancer. Hackshaw et al (28) estimated that the magnitude of the downward bias from background involuntary smoking exposure is on the order of 1.14, on the basis of results of studies on urinary cotinine levels among nonsmokers exposed to involuntary smoking and among unexposed nonsmokers. In a simulation, a hypothesized relative risk of 2.0 was reduced to 1.16, partly due to an inadequate assessment of exposure among those classified as exposed and partly to bias from background involuntary smoking exposure among those classified as unexposed (105).

Additional sources of underestimations of relative risk may derive from diagnostic misclassification of lung cancer cases. There is no clear evidence of a substantial effect of involuntary smoking exposure on cancers other than lung cancer. Therefore the inclusion of secondary cases of lung cancer or false lung cancers in a series of cases analyzed for involuntary smoking exposure would result in a bias towards the null. Although most of the recent studies of involuntary smoking and lung cancer have been based only on histologically or cytologically confirmed cases, this bias may have occurred in some of the early studies, which also included cases without histological or cytological confirmation. Even with histological or cytological confirmation, the differential diagnosis between primary lung cancer and secondary lung metastases may be difficult, particularly for adenocarcinomas. If it is assumed that the true relative risk for involuntary smoking is 1.20, the inclusion of 10% of cases of cancers other than the lung, with a relative risk of 1.0, would bias the observed relative risk (with 40% prevalence of exposure) to 1.18.

In conclusion, the epidemiologic evidence linking involuntary smoking exposure and the development of lung cancer represents an extraordinarily rich data set as compared with that for other environmental pollutants. The evidence has been under very detailed scrutiny, and several sources of bias have been proposed to explain the positive association. However, there are alternative sources of bias leading to an underestimation of the true association. While it is theoretically conceivable that bias and confounding may explain the excess risk of lung cancer reported among persons exposed to involuntary smoking, such a situation is not very plausible, and it is unlikely that it has occurred repeatedly in the many positive studies. The magnitude of the excess risk of lung cancer from exposure to involuntary smoking from the spouse or at the workplace, based on a comparison with persons who are exposed to background levels of this agent, is likely to be on the order of 15–25%. Substantial exposure is likely to result in higher risk.

Preliminary data from mechanistic studies provide some support for the evidence from questionnaire-based epidemiologic studies. It is unlikely that questionnaire-based studies, in the immediate future, will overcome completely the limitations that have been outlined to criticize the results of previous studies. On the other hand, studies based on biomarkers of past exposure (ie, serum cotinine measured in samples collected within prospective cohort studies) and on molecular targets of tobacco-related carcinogenesis (chiefly *p53* mutations) may provide important additional information.

Even if the excess risk from exposure to involuntary smoking is small, the large prevalence of exposure makes it an important environmental carcinogen. Estimates of the number of cases of lung cancer attributable each year to exposure to involuntary smoking (assuming a relative risk on the order of 1.2–1.3) were

in the range of 3000 for the United States (12), 1100 in the European Union (106), and 300 in Canada (107).

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References

1. United States Department of Health and Human Services (US DHHS). Ninth report on carcinogens. Washington (DC): US DHHS, 2000.
2. Blot WJ, McLaughlin JK. Passive smoking and lung cancer risk: what is the story now? J Natl Cancer Inst 1998;90: 1416–7.
3. Glantz S. Stanton Glantz on snuffing tobacco research (interview by Thomasine Kushner). Camb Q Health Ethics 1996; 5:415–21.
4. Trédaniel J, Boffetta P, Saracci R, Hirsch A. Environmental tobacco smoke and the risk of cancer in adults. Eur J Cancer 1993;29A:2058–68.
5. Boffetta P, Trédaniel J, Greco A. Risk of childhood cancer and adult lung cancer after childhood exposure to passive smoking: a meta-analysis. Environ Health Perspect 2000; 108:73–82.
6. Kawachi I, Colditz GA. Workplace exposure to passive smoking and risk of cardiovascular disease: summary of epidemiologic studies. Environ Health Perspect 1999; 107 suppl 6:847–51.
7. Jinot J, Bayard, S. Respiratory health effects of exposure to environmental tobacco smoke. Rev Environ Health 1996; 11:89–100.
8. Windham GC, Eaton A, Hopkin B. Evidence for an association between environmental tobacco smoke exposure and birthweight: a meta-analysis and new data. Paediatr Perinat Epidemiol 1999;13:35–57.
9. International Agency for Research on Cancer (IARC). Tobacco smoking. Lyon: IARC, 1986. IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans, vol 38.
10. International Agency for Research on Cancer (IARC). Overall evaluations of carcinogenicity: an updating of IARC monographs volumes 1 to 42. Lyon: IARC, 1987. IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans, suppl 7.
11. National Cancer Institute (NCI). Health effects of exposure to environmental tobacco smoke: the report of the California Environmental Protection Agency. Bethesda (MD): NCI, National Institutes of Health, US Department of Health and Human Services, 1999. NIH publication, no 99–4645.
12. United States Environmental Protection Agency (US EPA). Respiratory health effects of passive smoking: lung cancer and other disorders. US EPA, Office of Research and Development, 1992. Publication no EPA/600/6–90/006F.
13. Hoffmann D, Brunnemann, KD. Endogenous formation of N-nitrosoproline in cigarette smokers. Cancer Res 1983; 43:5570–4.
14. Cohen BS, Eisenbud M, Harley NH. Alpha radioactivity in cigarette smoke. Radiat Res 1980;83:190–6.
15. Al-Delaimy WK, Crane J, Woodward A. Questionnaire and hair measurement of exposure to tobacco smoke. J Exp Anal Environ Epidemiol 2000;10:378–84.
16. Matsukura S, Sakamoto N, Seino Y, Tamada T, Matsuyama H, Muranaka H. Cotinine excretion and daily cigarette smoking in habituated smokers. Clin Pharmacol Ther 1979;25: 555–61.
17. Wilcox RG, Hughes J, Roland J. Verification of smoking history in patients after infarction using urinary nicotine and cotinine measurements. BMJ 1979;25:555–61.
18. Williams CL, Eng A, Botvin GJ, Hill P, Wynder EL. Validation of students' self-reported cigarette smoking status with plasma cotinine levels. Am J Public Health 1979;69:1272–4.
19. Haley NJ, Axelrad CM, Tilton KA. Validation of self-reported smoking behavior: biochemical analyses of cotinine and thiocyanate. Am J Public Health 1983;73:1204–7.
20. Hill P, Haley NJ, Wynder EL. Cigarette smoking: carboxyhemoglobin, plasma nicotine, cotinine, and thiocyanate versus self-reported smoking data and cardiovascular disease. J Chronic Dis 1983;36:439–49.
21. Jarvis MJ, Russell MA. Measurement and estimation of smoke dosage to non-smokers from environmental tobacco smoke. Eur J Respir Dis Suppl 1984;133:68–75.
22. Wall MA, Johnson J, Jacob P, Benowitz NL. Cotinine in the serum, saliva, and urine of non-smokers, passive smokers, and active smokers. Am J Public Health 1988;78:699–701.
23. Friedman GD, Petitti DB, Bawol RD. Prevalence and correlates of passive smoking. Am J Public Health 1983;73:401–5.
24. Coultas DB, Howard CA, Peake GT, Skipper BJ, Samet JM. Salivary cotinine levels and involuntary tobacco smoke exposure in children and adults in New Mexico. Am Rev Respir Dis 1987;136:305–9.
25. Jenkins PL. Activity patterns of Californians: reported exposures to ETS. Presented at the Workshop on Health Effects of Environmental Tobacco Smoke, Oakland (CA), October 14, 1992.
26. Borland R, Pierce JP, Burns DM, Gilpin E, Johnson M, Bal D. Protection from environmental tobacco smoke in California: the case for a smoke-free workplace. JAMA 1992; 268:749–52.
27. Pirkle JL, Flegal KM, Bernert JT, Brody DJ, Etzel RA, Maurer KR. Exposure of the US population to environmental tobacco smoke: The Third National Health and Nutrition Examination Survey, 1988 to 1991. JAMA 1996;275:1233–40.
28. Hackshaw AK, Law MR, Wald NJ. The accumulated evidence on lung cancer and environmental tobacco smoke. BMJ 1997;315:980–8.
29. Wells AJ, English PB, Posner SF, Wagenknecht LE, Perez-Stable EJ. Misclassification rates for current smokers misclassified as nonsmokers. Am J Public Health 1998;88:1503–9.
30. Reynolds P. Epidemiologic evidence for workplace ETS as a risk factor for lung cancer among nonsmokers: specific risk estimates. Environ Health Perspect 1999;107(suppl 6):865–72.
31. Zhong L, Goldberg MS, Parent ME, Hanley JA. Exposure to environmental tobacco smoke and the risk of lung cancer: a meta-analysis. Lung Cancer 2000;27:3–18.
32. Riboli E, Preston-Martin S, Saracci R, Haley NJ, Trichopoulos D, Becher H, et al. Exposure of nonsmoking women to environmental tobacco smoke: a 10-country collaborative study. Cancer Causes Control 1990;1:243–52.
33. Hirayama T. Non-smoking wives of heavy smokers have a higher risk of lung cancer: a study from Japan. BMJ 1981;

282:183–5.
34. Trichopoulos D, Kalandidi A, Sparos L, MacMahon B. Lung cancer and passive smoking. Int J Cancer 1981;27:1–4.
35. Nyberg F, Agrenius V, Svartengren K, Svensson C, Pershagen G. Environmental tobacco smoke and lung cancer in nonsmokers — does time since exposure play a role? Epidemiology 1998;9:301–8.
36. Kreuzer M, Krauss M, Kreienbrock L, Jockel KH, Wichmann HE. Environmental tobacco smoke and lung cancer: a case-control study in Germany. Am J Epidemiol 2000;151: 241–50.
37. Boffetta P, Agudo A, Ahrens W, Benhamou E, Benhamou S, Darby SC, et al. Multicenter case-control study of exposure to environmental tobacco smoke and lung cancer in Europe. J Natl Cancer Inst 1998;90:1440–50.
38. Boffetta P, Agudo A, Ahrens W, Benhamou E, Benhamou S, Darby SC, et al. European multicentre case-control study of lung cancer in non-smokers: detailed results on exposure to environmental tobacco smoke. Lyon: International Agency for Research on Cancer (IARC), 1998. IARC technical report, no 33.
39. Der Simonian R, Laird N. Meta-analysis in clinical trials. Controlled Clin Trials 1986;7:177–88.
40. Egger M, Davey-Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997; 315:629–34.
41. Chan WC, Fung SC. Lung cancer in non-smokers in Hong Kong. In: Grundmann E, editor. Cancer campaign; vol 6 (cancer epidemiology). New York (NY): Gustav Fisher, 1982:199–202.
42. Correa P, Pickle LW, Fontham E, Lin Y, Haenszel W. Passive smoking and lung cancer. Lancet 1983;2:595–7.
43. Trichopoulos D, Kalandidi A, Sparros L. Lung cancer and passive smoking: conclusion of the Greek study. Lancet 1983; 2:677–8.
44. Buffler PA, Pickle LW, Mason TJ, et al. The causes of lung cancer in Texas. In: Mizell M, Corres P, editors. Lung cancer causes and prevention. New York (NY): Verlag Chemie International, 1984:83–99.
45. Kabat GC, Wynder EL. Lung cancer in nonsmokers. Cancer 1984;53:1214–21.
46. Lam WK. A clinical and epidemiological study of carcinoma of the lung in Hong Kong. Hong Kong: University of Hong Kong, 1985.
47. Wu AH, Henderson BE, Pike MC, Yu MC. Smoking and other risk factors for lung cancer in women. J Natl Cancer Inst 1985;74:747–51.
48. Lee PN, Chamberlein J, Alsderson MR. Relationship of passive smoking to risk of lung cancer and other smoking-associated diseases. Br J Cancer 1986;54:97–105.
59. Koo LC, Ho JH, Saw D, Ho CY. Measurements of passive smoking and estimates of lung cancer risk among non-smoking Chinese females. Int J Cancer 1987;39:162–9.
50. Pershagen G, Hrubec Z, Svensson C. Passive smoking and lung cancer in Swedish women. Am J Epidemiol 1987; 125:17–24.
51. Humble CG, Samet JM, Pathak DR. Marriage to a smoker and lung cancer risk. Am J Public Health 1987;77:598–602.
52. Lam TH, Kung IT, Wong CM, Lam WK, Kleevens JW, Saw D, et al. Smoking, passive smoking and histological types in lung cancer in Hong Kong Chinese women. Br J Cancer 1987;56:673–8.
53. Gao Y-T, Blot WJ, Zheng W, Ershow AG, Hsu CW, Levin LI, et al. Lung cancer among Chinese women. Int J Cancer 1987;40:604–9.
54. Brownson RC, Reif JS, Keefe TJ, Ferguson SW, Pritzl JA. Risk factors for adenocarcinoma of the lung. Am J Epidemiol 1987;125:25–34.
55. Geng G, Liang ZH, Zhang AY, et al. On the relationship between smoking and female lung cancer. In: Aoki M, Hisamichi S, Tominaga S, editors. Smoking and health. Amsterdam: Elsevier Science, 1988:483–6.
56. Shimizu H, Morishita M, Mizuno K, Masuda T, Ogura Y, Santo M, et al. A case-control study of lung cancer in nonsmoking women. Tohoku J Exp Med 1988;154:389–97.
57. Inoue R, Hirayama T. Passive smoking and lung cancer in women. In: Aoki M, Hisamichi S, Tominaga S, editors. Smoking and health. Amsterdam: Elsevier Science, 1988: 283–5.
58. Svensson C, Pershagen G, Klominek J. Smoking and passive smoking in relation to lung cancer in women. Acta Oncol 1989;28:623–9.
59. Janerich DT, Thompson WD, Varela LR, Greenwald P, Chorost S, Tucci C, et al. Lung cancer and exposure to tobacco smoke in the household. N Engl J Med 1990;323: 632–6.
60. Kalandidi A, Katsouyanni K, Voropoulou N, Bastas G, Saracci R, Trichopoulos D. Passive smoking and diet in the etiology of lung cancer among non-smokers. Cancer Causes Control 1990;1:15–21.
61. Sobue T. Association of indoor air pollution and lifestyle with lung cancer in Osaka, Japan. Int J Epidemiol 1990;19: S62–6.
62. Wu-Williams AH, Dai XD, Blot W, Xu ZY, Sun XW, Xiao HP, et al. Lung cancer among women in north-east China. Br J Cancer 1990;62:982–7.
63. Liu Z, He X, Chapman RS. Smoking and other risk factors for lung cancer in Wuanwei, China. Int J Epidemiol 1991; 20:26–31.
64. Brownson RC, Alavanja MCR, Hock ET, Loy TS. Passive smoking and lung cancer in nonsmoking women. Am J Public Health 1992;82:1525–30.
65. Stockwell HG, Goldman AL, Lyman GH, Noss CI, Armstrong AW, Pinkham PA, et al. Environmental tobacco smoke and lung cancer risk in nonsmoking women. J Natl Cancer Inst 1992;84:1417–22.
66. Liu Q, Sasco AJ, Riboli E, Hu MX. Indoor air pollution and lung cancer in Guangzhou, People's Republic of China. Am J Epidemiol 1993;137:145–54.
67. Kabat GC, Stellman SD, Wynder EL. Relation between exposure to environmental tobacco smoke and lung cancer in lifetime nonsmokers. Am J Epidemiol 1995;142:141–8.
68. Sun X-W, Dai X-D, Lin C-Y, et al. Passive smoking and lung cancer among nonsmoking women in Harbin, China. Lung Cancer 1996;14:S237.
69. Wang T-J, Zhou B-S, Shi J-P. Lung cancer in nonsmoking Chinese women: a case-control study. Lung Cancer 1996;14: S93–8.
70. Ko YC, Lee CH, Chen MJ, Huang CC, Chang WY, Lin HJ, et al. Risk factors for primary lung cancer among non-smoking women in Taiwan. Int J Epidemiol 1997;26:24–31.
71. Zaridze D, Maximovitch D, Zemlyanaya G, Aktakov ZN, Boffetta P. Exposure to environmental tobacco smoke and risk of lung cancer in non-smoking women from Moscow, Russia. Int J Cancer 1998;75:335–8.
72. Shen XB, Wang GX, Zhou BS. Relation of exposure to environmental tobacco smoke and pulmonary adenocarcinoma in non-smoking women: a case control study in Nanjing.

Oncol Rep 1998;5:1221–3.
73. Boffetta P, Ahrens W, Nyberg F, Mukeria A, Brüske-Hohlfeld I, Fortes C, et al. Exposure to environmental tobacco smoke and risk of adenocarcinoma of the lung. Int J Cancer 1999;83:635–9.
74. Zhong L, Goldberg MS, Gao YT, Jin F. A case-control study of lung cancer and environmental tobacco smoke among nonsmoking women living in Shanghai, China. Cancer Causes Control 1999;10:607–16.
75. Rapiti E, Jindal SK, Gupta D, Boffetta P. Passive smoking and lung cancer in Chandigarh, India. Lung Cancer 1999; 23:183–9.
76. Wang L, Lubin JH, Zhang SR, Metayer C, Xia Y, Brenner A, et al. Lung cancer and environmental tobacco smoke in a non-industrial area of China. Int J Cancer 2000;88:139–54.
77. Lee CH, Ko YC, Goggins W, Huang JJ, Huang MS, Kao EL, et al. Lifetime environmental exposure to tobacco smoke and primary lung cancer of non-smoking Taiwanese women. Int J Epidemiol 2000;29:224–31.
78. Zhou BS, Wang TJ, Guan P, Wu JM. Indoor air pollution and pulmonary adenocarcinoma among females: a case-control study in Shenyang, China. Oncol Rep 2000;7:1253–9.
79. Garfinkel L. Time trends in lung cancer mortality among nonsmokers and a note on passive smoking. J Natl Cancer Inst 1981;66:1061–6.
80. Hirayama T. Cancer mortality in nonsmoking women with smoking husbands based on large-scale cohort study in Japan. Prev Med 1984;13:680–90.
81. Butler TL. The relationship of passive smoking to various health outcomes among Seventh-day Adventists in California. Los Angeles (CA): University of California, 1988.
82. Hole DJ, Gillis CR, Chopra C, Hawthorne VM. Passive smoking and cardiorespiratory health in a general population in the west of Scotland. BMJ 1989;299:423–7.
83. Jee SH, Ohrr H, Kim IS. Effects of husbands' smoking on the incidence of lung cancer in Korean women. Int J Epidemiol 1999;28:824–8.
84. Garfinkel L, Auerbach O, Joubert L. Involuntary smoking and lung cancer: a case-control study. J Natl Cancer Inst 1985;75:463–9.
85. Fontham ET, Correa P, Reynolds P, Wu-Williams A, Buffler PA, Greenberg RS, et al. Environmental tobacco smoke and lung cancer in nonsmoking women: a multicenter study. JAMA 1994;271:1752–9.
86. Cardenas VM, Thun MJ, Austin H, Lally CA, Clark WS, Greenberg RS, et al. Environmental tobacco smoke and lung cancer mortality in the American Cancer Society's Cancer Prevention Study II. Cancer Causes Control 1997;8:57–64.
87. Boffetta P, Nyberg F, Agudo A, Benhamou E, Jöckel K-H, Kreuzer M, et al. Risk of lung cancer from exposure to environmental tobacco smoke from cigars, cigarillos and pipes. Int J Cancer 1999b;83:805–6.
88. Crawford FG, Mayer J, Santella RM, Cooper TB, Ottman R, Tsai WY, et al. Biomarkers of environmental tobacco smoke in preschool children and their mothers. J Natl Cancer Inst 1994;86:1398–402.
89. Tang D, Warburton D, Tannenbaum SR, Skipper P, Santella RM, Cereijido GS, et al. Molecular and genetic damage from environmental tobacco smoke in young children. Cancer Epidemiol Biomark Prev 1999;8:427–31.
90. Hernandez-Boussard TM, Hainaut, P. A specific spectrum of p53 mutations in lung cancer from smokers: review of mutations compiled in the IARC p53 database. Environ Health Perspect 1998;106:385–91.
91. Husgafvel-Pursiainen K, Boffetta P, Kannio A, Nyberg F, Pershagen G, Mukeria A, et al. p53 mutations and exposure to environmental tobacco smoke in a multicenter study on lung cancer. Cancer Res 2000;60:2906–11.
92. Vahakangas KH, Bennett WP, Castren K, Welsh JA, Khan MA, Blomeke B, et al. p53 and K-ras mutations in lung cancers from former and never-smoking women. Cancer Res 2001;61:4350–6.
93. Bennett WP, Alavanja MC, Blomeke B, Vahakangas KH, Castren K, Welsh JA, et al. Environmental tobacco smoke, genetic susceptibility, and risk of lung cancer in never-smoking women. J Natl Cancer Inst 1999;91:2009–14.
94. Nyberg F, Hou SM, Hemminki K, Lambert B, Pershagen G. Glutathione S-transferase mu1 and N-acetyltransferase 2 genetic polymorphisms and exposure to tobacco smoke in nonsmoking and smoking lung cancer patients and population controls. Cancer Epidemiol Biomark Prev 1998;7:875–83.
95. Malats N, Camus-Randon A-M, Nyberg F, Ahrens W, Constantinescu V, Mukeria A, et al. Lung cancer risk in nonsmokers and GSTM1 and GSTT1 genetic polymorphism. Cancer Epidemiol Biomark Prev 2000;9:827–33.
96. Husgafvel-Pursiainen K. Biomarkers in the assessment of exposure and the biological effects of environmental tobacco smoke. Scand J Work Environ Health 2002;28 suppl 2:21–29.
97. Lee PN, Forey BA. Misclassification of smoking habits as a source of bias in the study of environmental tobacco smoke and lung cancer. Stat Med 1996;15:581–605.
98. Nyberg F, Isaksson I, Harris JR, Pershagen G. Misclassification of smoking status and lung cancer risk from environmental tobacco smoke in never-smokers. Epidemiology 1997;8:304–9.
99. Nyberg F, Agudo A, Boffetta P, Fortes C, González CA, Pershagen G. A European validation study of smoking status and exposure to environmental tobacco smoke in non-smoking lung cancer cases and controls. Cancer Causes Control 1998;9:173–82.
100. National Research Council. Environmental tobacco smoke: measuring exposures and assessing health effects. Washington (DC): National Academy Press, 1986.
101. Puntoni R, Toninelli F, Zhankui L, Bonassi S. Mathematical modelling in risk exposure assessment of tobacco related lung cancer. Carcinogenesis 1995;16:1465–71.
102. Akiba S, Kato H, Blot WJ. Passive smoking and lung cancer among Japanese women. Cancer Res 1986;46:4804–7.
103. Hirayama T. Life-style and mortality: a large-scale census-based cohort study in Japan. 6. Basel: Karger, 1990.
104. Blot WJ, Fraumeni JF. Cancers of the lung and pleura. In: Schottenfeld D, Searle JG, Fraumeni JF, editors. Cancer epidemiology and prevention. 2nd edition. New York (NY): Oxford University Press, 1996:637–65.
105. Nyberg F, Pershagen G. Passive smoking and lung cancer: accumulated evidence on lung cancer and environmental tobacco smoke. BMJ 1998;317:347–8.
106. Trédaniel J, Boffetta P, Saracci R, Hirsch A. Non-smoker lung cancer deaths attributable to exposure to spouse's environmental tobacco smoke. Int J Epidemiol 1997;26:939–44.
107. Wigle DT, Collishaw NE, Kirkbride J, Mao Y. Deaths in Canada from lung cancer due to involuntary smoking. Can Med Assoc J 1987;136:945–51.