REVIEW

Exposure to environmental tobacco smoke and risk of lung cancer: the epidemiological evidence

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ABSTRACT: Exposure of nonsmokers to environmental tobacco smoke (ETS) is widespread in European countries, the most serious exposures occurring at home and in the workplace. Epidemiological studies available up to 1986 have been reviewed by several international and national authorities, which agreed in concluding that ETS exposure is causally related to lung cancer.

A number of epidemiological studies have been published since then, and have confirmed this association. The possibility of positive results due to bias has been envisaged; it seems, however, that such bias could not explain the whole excess of lung cancer. Few data are available on confounders, such as diet and previous history of lung disease, that might be responsible for the association; however, there is no evidence that they play an important role. Moreover, the biological plausibility of a causal association is supported by the similarity of the composition of ETS and active smoke.

The causal association between ETS exposure and lung cancer now seems well-established; however, its public health impact is still debated. Estimates are available from the United States, Canada, Australia, New Zealand and England.

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Tobacco smoking has been identified as the single most important source of preventable morbidity and premature mortality [1–5]. Evidence for a causal relationship between cigarette smoking and lung cancer incidence and mortality has been documented extensively since the 1960s. In the United States, cigarette smoking is expected to account for an estimated 87% of lung cancer mortality [6]. In 1995, 590,000 deaths from lung cancer are expected in the industrialized world, where lung cancer is the leading cause of cancer death [7]. During the last 15 yrs, attention has been focused on the potential health effects of environmental tobacco smoke (ETS). When this topic was first raised in the 1972 Report of the US Surgeon General [8], only a handful of studies had addressed this issue, and had provided very limited information. In 1986, two landmark reports by the US Surgeon General [9] and the US National Academy of Sciences [10] reached similar conclusions about the adverse health effects of involuntary smoking on healthy adults and children. They concluded, for the first time, that the involuntary inhalation of cigarette smoke by nonsmokers can cause disease, most notably lung cancer.

Among the other health effects which have been associated with ETS exposure are other types of cancer, non-neoplastic respiratory diseases, acute respiratory illnesses and cardiovascular diseases. They have been reviewed extensively [11–17]. The present review is

restricted to lung cancer, and will focus mainly on a discussion of studies published since 1986.

Epidemiological studies

At the time that the report of the Surgeon General [9] and other reports [10, 18, 19] were compiled, information on ETS and lung cancer was available from 13 epidemiological studies.

There had been two large cohort studies on ETS and lung cancer, from Japan [20] and the USA [21], and a smaller study from Scotland [22, 23] (table 1). A total of 367 nonsmoking lung cancer cases were diagnosed in these cohorts. The increase in relative risk (RR) from lung cancer for nonsmoking women married to smoking men was found to be small in the American study. In the Japanese cohort, the RRs were 1.4, 1.6, and 1.9 when the husbands were smokers of 1–14, 15–19, and ≥ 20 cigarettes-day⁻¹, respectively. The Scottish study reported an RR for lung cancer of 2.4 for persons with a partner who had ever smoked.

Eleven case-control studies [24–36] were reviewed by either the 1986 report of the Surgeon General [9] (table 2) or the National Research Council (NRC) report [10]. Four further studies provided very limited information, and were not considered by these two reports, nor will they be discussed in detail here [37–42].

Table 1. – Summary of design and results of prospective studies on ETS exposure and lung cancer

First author Country, Period [Ref.]	Population		Diagnosis verified	NS lung cancers n	Spouse's smoking		
	n	Sex			Exposure	RR	95% CI
HIRAYAMA Japan, 1966–1983 [20]	91,450	F	None	200	Exsmoker 1–14 cig·day ⁻¹ 15–19 cig·day ⁻¹ ≥20 cig·day ⁻¹	1.4 1.4 1.6 1.91	0.9–2.2 1.0–2.0 1.0–2.4 1.3–2.7
GARFINKEL USA, 1959–1972 [21]	176,739	F	+ first 6 yrs	153	<20 cig·day ⁻¹ ≥20 cig·day ⁻¹	1.27 1.10	0.9–1.9 0.8–1.6
HOLE Scotland, 1972–1985 [23]	3960 4037	M F	Cancer registry	6 M 8 F	PS vs controls	2.41	0.5–12.8

ETS: environment tobacco smoke; M: male; F: female; cig: cigarettes; RR: relative risk; PS: passive smokers; NS: non-smoking; 95% CI: 95% confidence interval.

Table 2. – Summary of design of case-control studies on ETS exposure and lung cancer included in the 1986 US Surgeon General's Report

First author Country, period [Ref.]	Cases	Controls	Histological diagnosis %	Adeno- carcinoma %	Spouse's smoking		
	n	n			Exposure	RR	95% CI
TRICHOPOULOS Greece, 1978–1982 [25]	77	225	65	0	Exsmoker 1–20 cigs·day ⁻¹ ≥21 cigs·day ⁻¹	1.9 1.9 2.5	0.9–4.1 1.0–3.7 1.7–3.8
CORREA USA [27]	30	313	97	54	1–40 pack-yrs ≥41 pack-yrs	1.5 3.1	0.6–3.8 1.1–8.5
CHAN China, 1976–1980 [26]	84	139	82	45	Spouse smoker	0.75	0.45–1.31
Koo China, 1981–1983 [30]	88	137	97	59	1–10 cigs·day ⁻¹ 11–20 cigs·day ⁻¹ ≥21 cigs·day ⁻¹	1.83 2.56 1.21	0.65–5.11 1.06–6.19 0.51–2.86
KABAT USA, 1976–1980 [28]	78	78	100	74 F 54 M	Spouse smoker	0.79 1.00	0.25–2.48 0.20–5.06
Wu USA, 1981–1982 [33]	29	62	100	100	1–20 yrs ≥21 yrs	1.4 1.2	0.4–4.9 0.4–3.7
GARFINKEL USA, 1971–1981 [32]	134	402	100	65	cigar/pipe <10 cigs·day ⁻¹ 10–19 cigs·day ⁻¹ ≥20 cigs·day ⁻¹	1.2 1.2 1.1 2.1	0.8–1.7 0.8–1.6 0.8–1.5 1.1–4.0
LEE UK, 1982–1983 [35]	47	96			Spouse smoker	1.03	0.41–2.55
AKIBA Japan, 1971–1980 [34]	103	380	57		1–19 cigs·day ⁻¹ 20–29 cigs·day ⁻¹ ≥30 cigs·day ⁻¹	1.3 1.5 2.1	0.7–2.3 0.8–2.8 0.7–2.5
PERSHAGEN Sweden, 1960–1980 [36]	67	347	99	57	Low High	1.0 3.2	0.6–1.8 1.0–9.5

For abbreviations see legend to table 1.

These studies have mainly compared individuals with higher ETS exposures to those with lower exposures. Because exposure to ETS is widespread [43], and it is difficult to construct a truly unexposed subgroup of the general population, observations were typically made

on lifelong nonsmoking women; those married to a smoker (referred to as exposed) were assumed to be at higher exposures than those not married to a smoker (unexposed). Six studies [20, 24, 27, 32, 34, 36] found a statistically significant increased risk when living

with a smoking spouse. Three of these studies [20, 27, 34] included female as well as male lung cancer patients.

The meta-analyses [10, 18, 19, 44] performed estimated that the relative risk for a nonsmoking woman living with a smoking man to present a lung cancer was around 1.35 (95% confidence interval (95% CI) 1.1–1.5), as compared to nonsmoking women living with nonsmoking men. SARACCI and RIBOLI [44] extended the review to include studies available up to 1987 [37, 45]. The overall RR was also 1.35 with 95% CI of 1.20 and 1.53. In other words, the results available up to 1987

suggested that nonsmokers exposed to ETS have an estimated 35% increased risk of lung cancer as compared to nonsmokers not exposed to ETS, and that the true value of this increase is likely to be 20–53%.

At least 14 new case-controls studies have been published since these reviews [45–58] (table 3). Seven further studies have also been published since 1987 [59–65], but they are not reviewed in detail here because of major methodological limitations.

The 14 recent case-control studies concentrated on ETS exposure through spousal smoking during adulthood. However, a growing number of studies have

Table 3. – Characteristics of the design of the case-control studies on ETS exposure and lung cancer published since 1986

First author Country, period [Ref.]	Nonsmoking cases n	Women %	Nonsmoking controls n	Source of controls	Case response %	Histological diagnosis %	Adeno- carcinoma %
BROWNSON USA, 1979–1982 [46]	23	83	66	Colon and bone marrow cancer	31 cases 61 controls	100	100
GAO China, 1984–1986 [47]	436 (246 living with smoking husband)	100	605 (375 living with smoking husband)	Population based	100	81	61
HUMBLE USA, 1980–1984 [45]	28	71	292	Population based	42	61	50
LAM China, 1983–1986 [48]	202	100	337	Population based	100	100	62.4
SHIMIZU Japan, 1982–1985 [49]	90	100	163	Hospitalized patients	100	100	77
SVENSSON Sweden, 1983–1986 [50]	38	100	120	Population based	100	100	58
KALANDIDI Greece, 1987–1989 [51]	91	100	120	Orthopaedic patients	100	86	
JANERICH USA, 1982–1984 [52]	191	76	191	Population based	67.5	100	
SOBUE Japan, 1986–1988 [53]	144	100	731	Hospitalized patients	100	100	78
WU-WILLIAMS China, 1985–1987 [54]	415	100	602	Population based	100	74	28
STOCKWELL USA, 1987–1991 [55]	210	100	301	Population based	33	100	61
BROWNSON USA, 1986–1991 [56]	432	100	1402	Population based	35	100	62
LIU China, 1983–1984 [57]	38	100	69	Hospitalized patients	100		
FONTHAM USA, 1986–1990 [58]	653	100	1253	Population + colon cancer	64	100	76

ETS: environmental tobacco smoke.

Table 4. – Sources of ETS exposure considered in the case-control studies on lung cancer published since 1986

First author [Ref.]	Childhood	ETS exposure during adulthood			
	Father/Mother	Spouse	Cohabitants	At work	Outside home
BROWNSON [46]	-	b, c	-	-	-
GAO [47]	a	b, c	-	-	-
HUMBLE [45]	-	b	-	-	-
LAM [48]	-	b, c, e	-	-	-
SHIMIZU [49]	b	b, c	b	a	-
SVENSSON [50]	a	a	a	a	-
KALANDIDI [51]	-	b, c	f	b, e	-
JANERICH [52]	b, f	b, f	b, f	a	a
SOBUE [53]	a	a	a	-	-
WU-WILLIAMS [54]	-	b, c	b	a	-
STOCKWELL [55]	f	f	f	f	a
BROWNSON [56]	b, c, d, e, g	b, c, d, e, g	b, c, d, e, g	b, c, d, e, g	b, c, d, e, g
LIU [57]	-	a, c	-	-	-
FONTHAM [58]	a, f	b, c, d, e, f	a	a, b	a

ETS: environmental tobacco smoke; a: smoker/nonsmoker; b: duration of exposure; c: number of cigarettes·day⁻¹; d: pack-yrs (PY); e: type of material smoked; f: smoker-yrs; g: product of total PY and average number of hours exposed per day to ETS in the home.

Table 5. – Results of the case-control studies on ETS exposure and lung cancer published since 1986

First author [Ref.]	Cases n	Nonsmoking controls	Type of exposure	RR	95% CI	Adjustment factors
BROWNSON [46]	19 F	47 F	≥4 h·day ⁻¹ *	1.68	0.39–2.97	A, I, O
GAO [47]	48	76	Smoking spouse (≥40 yrs)	1.7	1.0–2.9	A, E
HUMBLE [45]	28	292	Smoking spouse (all types of tobacco)	2.6	1.2–5.6 [#]	A, Ra
LAM [48]	202	337	Smoking spouse	1.65	1.16–2.35	
SHIMIZU [49]	90	163	Smoking: Husband Mother Husband's father	1.1 4.0 3.2		O, SP
SVENSSON [50]	38	120	Exposure as adult (at home and at work)	2.1	0.6–8.1	A
KALANDIDI [51]	91	120	Smoking spouse	1.92	1.02–3.59	A, D, E, Y
JANERICH [52]	191	191	Exposure as adult (≥75 smoker-yrs)	1.11	0.56–2.20	I, M, O, R
SOBUE [53]	144	731	Household members smoking in adulthood	1.50	1.01–2.22	H
WU-WILLIAMS [54]	415	602	Smoking spouse	0.7	0.6–0.9	A, E, S
STOCKWELL [55]	210	301	Smoking spouse (yes/no exposure)	1.6	0.8–3.0	A, E, Ra
BROWNSON [56]	432	1402(?)	Heavy exposure during adulthood**	1.8	1.1–2.9	A, P
LIU [57]	38	69	Smoking spouse (≥20 cig·day ⁻¹)	2.9	1.2–7.3	E, L, O
FONTHAM [58]	653	1253	Smoking spouse	1.29	1.04–1.60	A, Di, E, F I, O, Ra, S

[#]: 90% CI; (?): nonspecifically specified for the subgroup of lifelong nonsmokers; *: there was no specification of when and where ETS exposure occurred; **: semiquantitative evaluation. The study by LAM [46] did not include adjusted statistical analysis. Adjustment factors: A=age; E=education; I=income; O=occupation; Y=interviewer; D=energy intake; H=age at hospitalization; M=marital status; P=previous lung disease; R=religion; Ra=race, ethnicity; S=study area; SP=smoking status of the parents. For further abbreviations see legend to table 1.

addressed other sources of ETS exposure, namely during childhood, from household members other than the husband, at work, and in other situations outside the home. Moreover, more sophisticated indices of ETS exposure have been used; the complexity of the questionnaires used is presented in table 4. Exposure from the spouse was taken into account in all studies; nine studies considered other sources of ETS exposure, such as cohabitants [49–56, 58]; and parental exposure was considered by eight studies [47, 49, 50, 52, 53, 55, 58]. Two studies [50, 53] were only able to present results according to the smoking status of the spouse. Nine studies [45–49, 51, 54, 57, 58] presented analyses on ETS exposure, at least from the spouse, according to duration, quantity and type of tobacco smoked. Finally, four studies [52, 55, 56, 58] gave information on the number of smokers in the household and the duration of exposure, per year [52, 55, 58], or per day [56].

As a number of sources and levels of ETS exposure were recorded, many analyses were performed for each study. An overview of the results, according to exposure during adulthood, mainly from the spouse, is given in table 5.

A recent meta-analysis carried out by US Environmental Protection Agency [66] pooled the study results by country, giving six relative risks, and concluded that the link between ETS exposure and lung cancer among nonsmokers is highly significant ($p < 0.005$).

Methodological problems

It is highly unlikely that chance alone can explain the association between ETS and lung cancer. Even if the increase in risk seems to be no higher than 40%, the size of the populations which have been studied is large enough to exclude, with reasonable confidence, that it originated only by random statistical variation. Overall, 3,728 lifelong nonsmoking lung cancer cases have been included in the published studies; 2,991 of these (80%) were included after the 1986 reports, which had already drawn conclusions on the carcinogenic role of ETS. However, most of the studies which we have reviewed, especially the early ones, although suggestive of a positive effect, have had several deficiencies [67], which could substantially bias their results and make their interpretation problematical [68]. Bias is a systematic error in the design, conduct, analysis, or interpretation of a study that tends to produce an incorrect assessment of the nature of the association between an exposure or risk factor and the occurrence of the disease [69].

Misclassification of self-reported smoking status

Of particular concern are former and current smokers who report themselves as nonsmokers and, thus, may have been at higher risk for lung cancer than true nonsmokers, because of a history of smoking, rather than exposure to ETS. Therefore, a lung cancer effect

from active smoking may be contaminating, and falsely increasing, the evaluation of the risk of passive smoking, especially if this misclassification is more important among cases than controls [70–73]. Of particular concern, is the concordance of smoking habits in married couples: a woman who claims to be a nonsmoker is more likely to be, or to have been, an actual smoker if married to a smoker than if married to a nonsmoker. Conversely, misreporting among controls - and unrecognized exposure due to a degree of background ETS - tend to overstate the percentage classified as exposed to ETS. This artificially elevates the exposed percentage in controls relative to cases, thus, contributing to an underestimation of risk. A final possibility is that a nondifferential misclassification in the two groups leads to a point estimate that is biased towards the null value. It is plausible, that the first hypothesis is most commonly implied in the studies on ETS and lung cancer. Multiple sources of information can be utilized to validate nonsmoking status (medical record, physician, next-of-kin of the study subject, surrogate); study respondents can be questioned twice (at contact to set up the interview and at the beginning of the interview); a longitudinal study with repeated assessment of exposure might be able to identify lifetime nonsmokers more reliably and grade their exposure to passive smoking on a finer scale [74].

There have been a number of studies of the relationship of self-reported smoking habits to various biological indicators [75]. Nicotine and cotinine have received most attention, with cotinine being increasingly used as a short-term marker in epidemiological studies, because it has a longer half-life (20 h) than nicotine, is not susceptible to fluctuations during smoke exposure, and can be ascertained in urine and saliva [14]. There is a strong correlation, including a dose-response relationship between urinary cotinine levels and self-reported exposure to tobacco smoke [76–78].

The NRC Report [10], following the design of WALD *et al.* [18], assumed that up to 5% of those who have smoked are misclassified as lifelong nonsmokers. Such approximations, however, have been disputed [79, 80]. Using a different approach, the US Environmental Protection Agency (EPA) Report [66] made an adjustment on each study separately. Both results show that the potential bias due to smoker misclassification is highly unlikely to be responsible for the increased risks observed in the ETS lung cancer epidemiology studies.

The data available suggest that misclassification of smoking status is not likely to explain the excess risk. Fontham *et al.* [81] found that 0.8% of lung cancer cases, 2.6% of colon cases and 2% of population controls had very high cotinine/creatinine levels (100 ng·ml⁻¹), suggesting that they were current smokers. The International Agency for Research on Cancer (IARC) conducted a study in 13 centres and 10 countries, explicitly designed to elucidate this methodological issue [82]. They estimated the prevalence of unidentified smokers in populations of self-reported nonsmoking women on the basis of urinary cotinine measurements. The study found a very high correlation between self-reported

smoking habits and urinary cotinine, and indicated that no more than 2–3% of self-reported "nonsmokers" were likely to be smokers. Home exposure was the greatest determinant of urinary cotinine, with the smoking habits of the husband being the strongest predictor in quantitative terms. These data, which are in agreement with previously published results showing a greater effect of home exposure rather than of workplace exposure [83], reinforce the results obtained from the studies on ETS and lung cancer, which have focused mainly on the exposure from the spouse. It should be noted, however, that most of the evidence on misclassification of smoking status refers to women, and relatively few data are available on men. The same proportion of misclassified men would result in a stronger bias, given the higher average consumption of tobacco in men as compared to women.

The lack of quantitative ETS exposure data in many epidemiological studies has also been questioned. However, the more recent studies have included, as far as possible, a quantitative or semiquantitative evaluation of ETS exposure from the spouse and other sources, during childhood as well as adulthood (table 4), and their results are consistent with previous studies.

A more serious problem might be the misclassification of past smoking habits. In a study in two areas in Scotland, around 3,500 subjects were repeatedly asked about their smoking habits: around 4% of men, and 5–8% of those who admitted smoking, later claimed to be lifelong nonsmokers (L. Herbet, JS Fry, unpublished report cited by LEE [73]). However, one should bear in mind that ex-smokers have a lower risk of lung cancer than current smokers, and, therefore, are likely to introduce a smaller bias.

Finally, one must stress that because there is widespread exposure to ETS, the upward bias on the relative risk of lung cancer caused by smoker misclassification is counterbalanced by the downward bias from background ETS exposure to the supposedly unexposed group.

Misclassification of smoking status reported by next-of-kin

The existence of a differential in accuracy of obtaining ETS exposure histories between living and deceased subjects has been raised [84]. However, the methodology using next-of-kin to obtain data has been shown to provide ETS exposure information of high quality [36]. The information provided by surrogates has been comparable to that provided by the individuals themselves [81], as shown by the studies which compared the results with analyses limited to cases and controls interviewed in person [27, 34, 38, 46, 56, 58], whilst in the study by STOCKWELL *et al.* [55], the risk estimates were considerably lower when a surrogate respondent other than the patient's husband provided information on exposure. Therefore, from the scarce evidence available, it does not seem that this type of bias can explain the positive results.

Recall bias

A further factor that must be considered is recall bias, *i.e.* the possibility that a nonsmoking woman, or a respondent, with lung cancer will falsely inflate the ETS exposure from the spouse in an attempt to find a causal explanation for her disease. This point was particularly addressed in the study by FONTHAM *et al.* [58, 81]. Two control groups, one with another type of cancer and one from the general population, were selected for case-control comparisons. It was hoped that differential recall between cases and other type cancer controls would be minimized, since both groups were similarly motivated to recall earlier exposure. It appeared that the pattern of risk was the same, when cases were compared to colon cancer or population controls.

Misdiagnosis of primary lung cancer

Two kinds of problem are to be discussed concerning the clinical and pathological diagnosis of lung cancer. Firstly, the fact that, in some studies, no histological verification exists that the patients were suffering from primary lung cancer. This was especially the case in earlier studies. However, in the studies by TRICHOPOULOS [24] and GARFINKEL *et al.* [32], the RR associated with ETS were similar when calculations were restricted to histologically confirmed cases. Most recent studies are based only on histologically confirmed cases (table 3), and some of them [45, 58] have also included a review of cases by experienced pathologists.

The second problem is the distinction between a primary neoplasm and metastases coming from an extrapulmonary cancer [86], as much as adenocarcinomas are the most frequent lung tumours in lifelong nonsmokers. However, a diagnosis of primary lung cancer in a lifelong nonsmoker is a fairly rare situation, which involves the physician in the search for a primary extrapulmonary tumour, such as breast cancer in females, since treatment and prognosis are very different. Moreover, if secondary tumours are not excluded from the case series, the RR associated with any factor that causes primary lung carcinomas are likely to be underestimated (unless the extrapulmonary cancer is associated with ETS exposure more strongly than lung cancer).

Publication bias

Publication bias has been questioned, in particular, by MANTEL [87], *i.e.* papers with nonsignificant or negative results are either not submitted or not accepted for publication in the scientific literature. However, publication bias can be active in either direction, *i.e.* the desire to minimize the impact of false positive assertions could result in a preference for publishing findings that refute a previous claim, rather than confirmatory results [88]; this could have been the case when the supposed association is weak, as is that of ETS exposure and lung cancer. Using the method of the funnel plot, *i.e.* risk

estimates are plotted against a measure of study size, in the absence of publication bias, the risk estimates should be symmetrically distributed around the true value, with decreasing variability as study size increases (showing a picture of a funnel); in 1988, VANDENBROUCKE [89] estimated that there was only a possibility of publication bias in studies on men. However, after collecting unpublished data on passive smoking, WELLS [90] concluded that it is unlikely that publication bias has any substantial effect on the RR that have been calculated from published reports for passive smoking either for men or women. WOODWARD and McMICHAEAL [91] were unable to find any unpublished studies, and concluded on the absence of publication bias of practical effect.

Confounding factors

Very few data are available on the possible confounding effect of risk factors for lung cancer other than ETS [92, 93]. Confounding is the phenomenon whereby an association between two study variables, usually the exposure and the disease outcome it is thought to cause, is over- or underestimated due to the effect of a third variable, the confounder [94]. Excluding the study by LAM *et al.* [48], all recent studies have taken some possible confounding factors into account in multiple logistic analyses (table 5): age, ethnicity, diet, occupational exposures, education, income, religion and marital status have been examined.

Diet may be an important confounder in studies of passive smoking and lung cancer [95]. Smokers have been shown to follow a diet that is rich in fat and poor in vegetables and fruits [96, 97], which in turn is associated with an elevated risk of lung cancer [98, 99]. If nonsmokers who live with smokers share similar dietary habits [100, 101], their risk of lung cancer could be increased by diet alone. Limited data are available to address this issue. Many of the published studies have included questions on diet [27, 28, 31, 33, 34, 37, 47, 49–51, 54, 56, 58], but only three [33, 51, 58] have attempted to adjust for diet and suggested no confounding effect.

Occupation and social class must also be taken into account. Indeed, it has been suggested that smokers are over-represented in industrial jobs, and that there is a distinct pattern linking the social class and occupation of members of the household to different smoking patterns [102]. It is, therefore, conceivable that nonsmokers living with smokers may be more frequently exposed to toxic materials that are carried into the home by family members with jobs involving exposure to hazardous substances, or that ETS exposure at the workplace may be a marker of exposure to other carcinogens. Also, families of industrial workers are likely to be located in areas subjected to higher levels of air pollutants, that could be related to the occurrence of lung cancer [103].

Questions on occupational exposures [24, 27, 28, 33–35, 37, 45, 46, 49, 54, 56, 58], as well as on socio-economic

and demographic characteristics [24, 28, 32, 35, 36, 46–48, 51, 54, 56, 62, 63] were included in many studies. Exposure to indoor air pollution (including radon) [6, 104] might play an important role in the causation of lung cancer, thus, reducing the possible effect of ETS exposure [26, 33, 47, 54, 57, 63].

However, there is no convincing evidence that these potential confounding factors could have affected the results of these studies.

ETS and lung cancer: proof of causation

Consistency and strength of association. In spite of the varying characteristics of each study, the three cohort studies (table 1), and 20 of the 23 case-control studies (tables 2 and 5) showed a weak positive association, with statistical significance being achieved in about half of the studies. The evidence remains statistically significant and conclusive after adjustments for smoker misclassification; for example, the summary estimate of relative risk from nine case-control plus two cohort studies, from the United States, is 1.19 (90%CI 1.04–1.35; $p < 0.05$); rising to 1.59 after adjusting for background ETS sources (1.34 for nonspousal exposures only) [66].

Specificity. In the case of ETS exposure, the proportion of adenocarcinomas (tables 2 and 3) is superior to that currently noted for male active smokers; whereas, adenocarcinoma is the most frequent cancer type in females (smokers as well as nonsmokers) [105]. As ETS-related lung cancers occur mainly in females, the criterion for specificity is not completely fulfilled, excluding the fact that the proportion of adenocarcinomas in lung cancer of lifelong nonsmoking females is higher than that in current or former smokers.

Coherence. The fact that similar risk estimates have been found in populations which are genetically different, and are exposed to different environmental factors, argues in favour of a general association between ETS and lung cancer.

Dose-response relationship. Based on the firmly established causal association of lung cancer with active smoking, with a dose-response relationship down to low doses, passive smoking is considered likely to have a similar effect on the lung. Two of the three prospective studies examined a dose-response relationship, which existed only in the Japanese study [20] (table 1). Seven of the 10 case-control studies included in the 1986 reports did so, and found a positive relationship in five cases [24, 27, 32, 34, 36] (table 2). Considering only the exposure during adulthood, especially from the spouse, eight of the more recent studies also looked for a potential relationship with seven positive findings (table 6). Although relatively weak, these dose-response studies have suggested the existence of a true and relatively consistent exposure-response relationship, especially when considering the level of smoking by the spouse, but a less consistent relationship with years

Table 6. — Dose response relationship between lung cancer risk and ETS exposure in adulthood (mainly from the spouse) in case-control studies published since 1986

Author [Ref.]	Type of exposure	RR	95% CI
BROWNSON [46]	0–3 h-day ⁻¹	1.00	
	≥4 h-day ⁻¹	1.68	0.39–2.97
GAO [47]	<20 yrs	1.0	
	20–29 yrs	1.1	0.7–1.8
	30–39 yrs	1.3	0.8–2.1
	≥40 yrs	1.7	1.0–2.9
HUMBLE [45]	≤20 cigs-day ⁻¹	2.0	0.9–4.6*
	>20 cigs-day ⁻¹	1.6	0.5–4.9*
	≤26 yrs	1.9	0.7–4.7*
	>26 yrs	1.8	0.7–4.5*
SVENSSON [50]	At home or at work	1.2	0.4–2.9
	At home and at work	2.1	0.6–8.1
JANERICH [52]	1–24 smoker-yrs	0.64	0.34–1.21
	25–49 smoker-yrs	0.81	0.45–1.45
	50–74 smoker-yrs	1.00	0.52–1.93
	≥75 smoker-yrs	1.11	0.56–2.20
STOCKWELL [55]	<22 smoker-yrs	1.6	0.8–3.2
	22–39 smoker-yrs	1.4	0.7–2.9
	≥40 smoker-yrs	2.4	1.1–5.3
BROWNSON [56]	0–15 pack-yrs	0.7	0.5–1.1
	15–40 pack-yrs	0.7	0.5–1.0
	≥40 pack-yrs	1.3	1.0–1.7
	0–50 pack-yrs × h-day ⁻¹	0.7	0.5–1.0
	50–175 pack-yrs × h-day ⁻¹	0.8	0.5–1.1
	>175 pack-yrs × h-day ⁻¹	1.3	1.0–1.7
LIU [57]	1–19 cigarettes-day ⁻¹	0.7	0.23–2.20
	≥ 20 cigarettes-day ⁻¹	2.9	1.20–7.30
FONTHAM [58]	<15 pack-yrs	1.02	0.80–1.31
	15–39 pack-yrs	1.02	0.76–1.36
	40–79 pack-yrs	1.34	0.98–1.83
	≥80 pack-yrs	1.87	1.06–3.31
	1–15 yrs	0.98	0.76–1.27
	16–30 yrs	1.23	0.93–1.63
	>30 yrs	1.23	0.94–1.61

*: 90% CI. For abbreviations see legend to table 1.

of exposure [106]. The low reliability of self-reported duration of exposure to ETS could explain the inability of several studies to detect a significant duration-response relationship [107]. Recent studies are of particular interest in this respect, because they include questions on ETS during childhood, with one recently published paper showing a risk linked to childhood exposure [52].

Biological plausibility. Combustion of tobacco products indoors contaminates the air with nearly 5,000 chemicals [1]. The sidestream smoke has been documented to contain virtually all the same carcinogenic compounds that have been identified in the mainstream smoke inhaled by smokers [75, 108]. Since sidestream smoke does not pass through the lung filter, it contains up to 100 times the weight of carcinogens of mainstream smoke. Consequently, elevated levels of carcinogens are found in the blood [109] and urine [110] of passive smokers. It is, therefore, biologically plausible that passive smoke exposure causes lung cancer,

because of this presence of carcinogens to which there is no established lower threshold level of exposure for the development of lung cancer.

In addition, a recent autopsy study [111] showed that epithelial, possibly precancerous lesions from bronchi and pulmonary parenchyma, were present significantly more among deceased nonsmoking women married to smokers rather than to nonsmokers; moreover, the Reid Index (which evaluates the gland and bronchial wall thickness) was also higher among nonsmoking women married to smokers in comparison with those married to nonsmokers.

Animal evidence. There are no lifelong animal inhalation studies of ETS, but one study [112] was designed to test the hypothesis that exposure to ETS in the home could constitute a risk factor for lung cancer in dogs. Such an approach to the problem is interesting because of the relative freedom from confounding factors, such as occupational exposure, and the dog's shorter life span and restricted residential mobility. A weak relationship was found for exposure to a smoker in the home (RR=1.6; 95% CI 0.7–3.7). New epidemiological studies in pet animals could add to the understanding of ETS effects in human populations.

Analogy. In the case of ETS and lung cancer, as the chemical components are the same as those of mainstream smoke, some of the effects of ETS must be analogous to those of active smoking. Thus, the risk observed at higher levels of exposure can be extrapolated at low doses; the regression line of risk for lung cancer according to amount of cigarette smoke suggests a log-linear relationship, which implies a small but existent risk for exposure to very low levels of tobacco smoke [113].

In summary, all the available data seem to fulfil at least to a reasonable degree, the criteria needed to accept a causal link between ETS and lung cancer among lifelong nonsmokers.

Public health impact

The individual risk of lung cancer from exposure to ETS does not have to be very large to translate into a significant health hazard, because of the large number of smokers and the widespread presence of ETS. The size of this effect, in terms of numbers of lung cancers caused in different populations, is still a matter of research and debate. The proportion of lung cancer cases among nonsmokers that could be attributed to ETS has been estimated to be, in western countries, about 20–30% [114]. Estimates are available on the number of lung cancer cases caused by ETS exposure in Canada [115], Australia [116], New Zealand [117], the USA [10, 66, 118–122] and England [123].

Recently, the EPA Report [66] gave an estimate of 3,060 lung cancer deaths per year, in US nonsmokers aged 35 yrs and over, attributable to ETS.

No precise estimation of the risk is yet currently

available for the European Community. JARVIS [123] suggested a figure of about 200 deaths per year from lung cancer in nonsmokers attributable to ETS exposure in Britain. It is, therefore, reasonable to assume that this risk corresponds, as a minimum, to several hundreds deaths from lung cancer every year in the European Community.

These consistent data, together with the previous reports and fundamental data comparing the chemical composition of ETS with that of mainstream smoke, led the US National Institute for Occupational Safety and Health to consider ETS as a potential occupational carcinogen in the workplace [124], and the EPA [66] to consider ETS as a human carcinogen.

As medical evidence on the harmful effects of ETS has accumulated since the early 1970s, there has been a parallel increase in legal action [91, 125–129] following the emergence of nonsmokers' rights. Following the example of France, which has recently promoted a law prohibiting advertising, and restricting smoking at work and public places to designated areas, one can support a common action of the European Community to protect nonsmokers.

The causal relationship between ETS and lung cancer seems now to be clearly established [130]. Even though ETS poses a lower risk than active smoking, it yields an appreciable number of deaths, because of the large number of potentially exposed individuals. On the assumption that the observed summary rate ratio of 1.3 for lung cancer is causal, the lifetime attributable fraction for lifelong nonsmokers has been calculated to be 390–990 per 100,000 deaths [131]. The magnitude of this health risk in different settings, especially at work, must be more precisely calculated. However, enough is already known (in conjunction with data on active smoking) to justify action and the restriction or prohibition of smoking [132, 133], especially in areas where tobacco consumption is still high, as in most European countries.

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