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# Environmental Tobacco Smoke and the Risk of Cancer in Adults

**Jean Trédaniel, Paolo Boffetta, Rodolfo Saracci and Albert Hirsch**

**The apparent effect of environmental tobacco smoke (ETS) exposure on cancer risk has become an important social and political issue. The risk of cancer in non-smokers is often the main reason for prohibiting or restricting smoking in public places. A number of epidemiological studies have shown an association between ETS exposure and lung cancer. However, the strength of this association has still to be estimated. Only a few studies have reported on ETS and cancer from sites other than the lung in adults. No definite conclusions can be drawn at present from a critical review of the epidemiological evidence, but the suggestion of an association is present for sinonasal cancer, while bladder cancer does not seem to be associated to ETS exposure. Positive studies are available for cancers from other sites, including the breast, the uterine cervix and the brain, but these are difficult to interpret.**
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## INTRODUCTION

CIGARETTE SMOKING has been identified as the single most important source of preventable morbidity and premature mortality [1–6]. The production of lung cancer is by far the most important carcinogenic effect quantitatively, as lung cancer is now the most common fatal cancer throughout the world [7], and is expected to increase further in the future [8]. Moreover, further evidence has linked tobacco smoking with cancers of the larynx, oral cavity, oesophagus, pancreas, bladder, kidney, stomach and the uterine cervix [9].

Passive smoking, involuntary smoking and exposure to environmental tobacco smoke (ETS) are used synonymously to describe the involuntary exposure of non-smokers to tobacco combustion products generated by smokers. ETS comprises the amount of tobacco smoke which is not inhaled by the smoker (sidestream smoke), as well as the portion of inhaled smoke

Correspondence to J. Trédaniel.
J. Trédaniel, P. Boffetta and R. Saracci are at the Unit of Analytical Epidemiology, International Agency for Research on Cancer, 150 Cours Albert Thomas, 69372 Lyon, Cedex 08, France; and A. Hirsch is at the Service de Pneumologie, Hôpital Saint-Louis, 1 Avenue Claude Vellefaux, 75475 Paris, Cedex 10, France.
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which is not retained in the smoker's lung and is exhaled into the environment. Although the exposures to active smoke and ETS are not identical, the latter appears to include inhalation of most tobacco combustion by-products, especially the carcinogens [2, 10–13].

During the past 15 years, attention has been focused on the potential health effects of ETS [14–17]. When this topic was first raised in the 1972 Report of the US Surgeon General [18], only a handful of studies had addressed this issue, and these had provided very limited information. The 1984 Report on Chronic Obstructive Lung Disease [19] devoted more attention to ETS. In 1986, two landmark reports by the US Surgeon General [20] and the US National Academy of Sciences [21] reached similar conclusions about the adverse health effects of involuntary smoking on healthy adults and children; they concluded for the first time that involuntary inhalation of tobacco smoke by non-smokers can cause disease, most notably lung cancer. There is also cumulative evidence that ETS is harmful for children [22, 23]. On the contrary, the effects of ETS on non-neoplastic respiratory diseases in adults are still a matter of discussion [22–24]. Finally, concordant data are supportive of the hypothesis that ETS may cause coronary heart disease [25, 26].

The potential carcinogenic effects of ETS on organs other than the lungs has not been fully clarified. Several reviews of the literature on ETS have addressed some aspects of this problem, but a recent comprehensive review is lacking, particularly as ETS exposure in the workplace assumes increasing importance as an occupational health issue [16, 27–29]. One might expect to find that for smoking-related sites, the cancer risk in individuals passively exposed to cigarette smoke may approach the risk found for very light smokers; risk from ETS exposure might also be expected to be much lower than that from direct smoking. On the other hand, some chemicals appear in higher concentrations in sidestream smoke than in mainstream smoke, making the exposure from ETS qualitatively different (Table 1). The health consequences of ETS exposure may, therefore, differ from those of direct smoking: these chemicals, many of which are known carcinogens, might lead to increased risks for cancer at sites not shown to be related to direct exposure to cigarette smoke. This paper will review the epidemiological evidence between ETS exposure and cancer in adults, with special emphasis on cancers in organs other than the lungs.

*Table 1. Chemicals in tobacco smoke which are carcinogenic, or probably carcinogenic to humans, and ratio of sidestream smoke (SS) to mainstream smoke (MS) concentration* [2]

| | SS/MS |
|---|---|
| Established human carcinogens | |
| 4-Aminobiphenyl | 31 |
| Arsenic | — |
| Benzene | 5–10 |
| Chromium compounds | — |
| Nickel compounds | 13–30 |
| Vinyl chloride | — |
| Probable human carcinogens | |
| Benzo[*a*]pyrene | 2–4 |
| Cadmium | 7 |
| Dibenz[*a*,*h*]anthracene | 2–4 |
| Formaldehyde | 1–50 |
| *N*-Nitrosodiethylamine | 40 |
| *N*-Nitrosodimethylamine | 20–100 |

## REVIEW OF THE STUDIES

Active smoking is an important cause not only of lung cancer, but also of cancer of the larynx, oral cavity, oesophagus, pancreas, bladder, kidney, stomach and uterine cervix [2, 9]. The first emphasis in this article is thus on smoking-related cancers (Tables 2 and 3), because these might be more plausibly associated with ETS exposure. However, there may be effects of ETS exposure on the risk of developing other cancers [21], which are summarised in Table 4.

*Lung cancer*

At the time the Surgeon General's Report [20] and other reports [20, 21, 31] were compiled, information on ETS and lung cancer was available from 13 studies. There had been three cohort studies on ETS and lung cancer, from Japan [32], the U.S.A. [33] and Scotland [34, 35]. A total of 367 non-smoking lung cancer cases were diagnosed in these cohorts. The increase in relative risk (RR) from lung cancer for non-smoking women married to smoking men was found to be small in the American study: 1.1 for women with husbands smoking 20 or more cigarettes per day compared with wives of non-smoking husbands. In the Japanese cohort, the RR were 1.42, 1.58 and 1.91 when the husbands were smokers of 1–14, 15–19 or 20 or more cigarettes per day, respectively. The Scottish study, which was smaller, reported a RR for lung cancer of 2.41 for persons (of both genders) with a partner who had ever smoked.

Ten case–control studies [36–48] were reviewed by the 1986 Surgeon General's Report. One further study, available in 1986 [49], was not included in this report. On the contrary, it was considered by the National Research Council (NRC) Report [21], which in turn excluded one of the previous studies [44] for the reason that raw data were not sufficiently detailed. Further studies [50–54] provided limited information and were not considered by these two reports.

The meta-analyses [21, 30, 31, 55] which were performed at that time estimated that the relative risk for a non-smoking woman living with a smoking man to present a primary lung cancer was approximately 1.35 [95% confidence interval (C.I.) 1.1–1.5], compared with non-smoking women living with non-smoking men.

At least 13 new case–control studies [56–68] have been published since these reviews. Seven further studies provide limited information [69–75]. The 13 recent case–control studies, like the previous ones, concentrated on ETS exposure from spouses smoking during adulthood. However, a growing number of studies have 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 elements of appreciation have been used. An overview of the results, according to the exposure during adulthood, mainly from the spouse, is given in Table 2.

Due to these data, and following the results of eight meta-analyses [21, 30, 31, 55, 76–79] which were performed on all these studies, the US National Institute for Occupational Safety and Health recommended in 1991 that ETS exposure be regarded as a potential occupational carcinogen, and that ETS exposure be reduced to the lowest feasible concentration [80]. Recently, the US Environmental Protection Agency pooled the study results by country, giving six RR, and concluded that the link between ETS exposure and lung cancer among non-smokers is highly significant ($P < 0.005$) [23].

*Table 2. Results of case–control studies, according to exposure during adulthood, on ETS exposure and lung cancer published since* 1986

| Author (country, year of publication) | No. of cases | No. of non-smoking controls | Type of exposure | RR | 95% C.I. | Ref. |
|---|---|---|---|---|---|---|
| Humble *et al.* (U.S.A., 1987) | 28 | 292 | Smoking spouse (all types of tobacco) | 2.6 | 1.2–5.6* | 56 |
| Brownson *et al.* (U.S.A., 1987) | 19F | 47F | ⩾ 4 h/day ‡ | 1.68 | 0.39–2.97 | 57 |
| Gao *et al.* (China, 1987) | 48 | 76 | Smoking spouse (⩾ 40 years) | 1.7 | 1.0–2.9 | 58 |
| Lam *et al.* (China, 1987) | 202 | 337 | Smoking spouse | 1.65 | 1.16–2.35 | 59 |
| Shimizu *et al.* (Japan, 1988) | 90 | 163 | Smoking husband | 1.1 | | 60 |
| | | | Smoking mother | 4.0 | | |
| | | | Smoking husband's father | 3.2 | | |
| Svensson *et al.* (Sweden, 1989) | 38 | 120 | Exposure as adult (at home and at work) | 2.1 | 0.6–8.1 | 61 |
| Kalandidi *et al.* (Greece, 1990) | 91 | 120 | Smoking spouse | 1.92 | 1.02–3.59 | 62 |
| Janerich *et al.* (U.S.A., 1990) | 191 | 191 | Exposure as adult (⩾ 75 smoker-years) | 1.11 | 0.56–2.20 | 63 |
| Sobue (Japan, 1990) | 144 | 731 | Household members smoking in adulthood | 1.50 | 1.01–2.22 | 64 |
| Wu-Williams *et al.* (China, 1990) | 415 | 602 | Smoking spouse | 0.7 | 0.6–0.9 | 65 |
| Fontham *et al.* (U.S.A., 1991) | 420 | 351/780 | Smoking spouse | 1.29 | 0.99–1.69 | 66 |
| Stockwell *et al.* (U.S.A., 1992) | 210 | 301 | Smoking spouse (yes/no exposure) | 1.6 | 0.8–3.0 | 67 |
| Brownson *et al.* (U.S.A., 1992) | 432 | 1402† | Heavy exposure during adulthood § | 1.8 | 1.1–2.9 | 68 |

RR, relative risk; C.I., confidence interval; F, female. *90% C.I. †Non-specifically specified for the subgroup of never-smokers. ‡There was no specification of when this exposure occurred. §Semi-quantitative evaluation.

*Bladder cancer* (*Table* 3)

Kabat and coworkers examined a variety of possible risk factors for bladder cancer in a group of 152 cases of bladder cancer in lifetime non-smokers, recruited from six cities in the U.S.A. [81]. Information on the spouse's smoking status was asked of those individuals who had ever been married. However, because questions on passive smoking were only added in the middle of the study, spouse's smoking status was available for only 58% of the cases and controls. Moreover, information on ETS exposure at home and at work was available for only 21% of the studied subjects. No significant association was found either for spouse's smoking or for other ETS source exposure.

Burch and co-authors conducted a large case–control study on the association between tobacco and bladder cancer [82]. In all, 826 histologically confirmed cancer cases and 792 controls were recruited in Alberta and south-central Ontario, Canada. 61 patients were lifelong non-smokers. There was no evidence for an effect of passive smoking, even when risk was examined by duration of exposure, or when those who had been exposed both at work and at home were compared with those reporting no exposure.

*Cervical cancer* (*Table* 3)

Buckley and colleagues found a 2-fold increase in risk of cervical cancer among women whose husbands smoked [83]. However, smoking habits of the women were not controlled for. Brown and colleagues compared 22 patients with *in situ* and 11 patients with invasive carcinoma of the cervix with 29 controls who had had hysterectomies for reasons other than cancer [84]. Husbands of *in situ* patients smoked more than those of the invasive patients. There was no significant difference according to personal smoking status between cancer patients and the control group. Hellberg and co-workers found that, although smoking by the male partner was correlated with cervical cancer, this relationship disappeared following adjustment for the smoking habits of the woman [85]. However, this study did not have a sufficient sample size to assess the effect of male partners who smoked on non-smoking cases.

In a case–control study [54] based on 56 cases Sandler and coworkers found a 2-fold risk for cervical cancer among non-smoking individuals passively exposed to cigarette smoke. Risk appeared to be greatest among younger women.

Slattery and colleagues conducted a case–control study in the urban areas of Utah between 1984 and 1987 [86]. Women who had a first, primary cancer diagnosis of *in situ* (234 women) or invasive squamous cell carcinoma of the cervix (36 cases) were interviewed. 81 patients had never smoked. As results were similar for carcinoma *in situ* and invasive cervical cancer, these were combined. ETS exposure resulted in an increased risk of cervical cancer for both smokers and non-smokers; for example, the risk estimate adjusted for age, educational level, church attendance, sexual activity and personal smoking, associated

*Table 3. Summary of case–control studies on ETS exposure and active smoking-related cancers*

| Author (year, country) | Never smoked patients | Type of cancer | Results | Reference |
|---|---|---|---|---|
| Kabat *et al.* (1986, U.S.A.) | 152 | Bladder | % of smoking wife: 30.6% cases, 36.5% controls; % of smoking husband: 68.6% cases, 64.8 controls | [81] |
| Burch *et al.* (1989, Canada) | 61 | Bladder | ETS exposure at home: RR (95% C.I.) Males 0.94 (0.45–1.95), Females 0.75 (0.38–1.71); ETS exposure at work: RR (95% C.I.) Males 0.97 (0.50–1.91), Females 0.93 (0.48–1.79) | [82] |
| Sandler *et al.* (1985, U.S.A.) | 56 | Cervix | RR (95% C.I.) $P < 0.05$: All cases 2.1 (1.2–3.9); < 50 years 2.9; ⩾ 50 years 0.9 | [54] |
| Slattery *et al.* (1989, U.S.A.) | 81 | Cervix | All ETS exposures (hours/day) RR (95% C.I.): None 1.00; 0.1–0.9 1.14 (0.45–2.94); 1.0–2.9 1.57 (0.52–4.73); ⩾ 3.0 3.43 (1.23–9.54) | [86] |

RR, relative risk; C.I. confidence interval.

with 3 or more hours per day of ETS exposure was 2.96 (95% C.I. 1.25–7.03). Moreover, the risk associated with this duration of ETS exposure was greater in women who were non-smokers than in women who smoked.

*Nasal sinus cancer* (*Table* 4)

Hirayama, as part of his long-term prospective study of 33 000 non-smoking Japanese wives aged 50–59 years enrolment, on the health consequences of cigarette smoking [32, 87], suggested an increased mortality from nasal sinus cancer among women whose husbands smoked, as compared with non-smoking wives of non-smoking husbands as the reference group. Moreover, a positive dose–response relationship was observed.

Fukuda and Shibata performed a case–control study of squamous cell neoplasms of the maxillary sinus in Hokkaido, Japan [88]. 35 women were lifelong non-smokers. A statistically significant linear trend was observed for the number of smokers in the household as an index of domestic exposure to cigarette smoke.

*Breast cancer* (*Table* 4)

A possible effect of ETS exposure on female breast cancer has been proposed, especially by Horton [89, 90]. This author correlated male lung cancer incidence with female breast cancer incidence in various countries and various parts of the U.S.A. and suggested that ETS exposure could play the role of initiator and/or early-stage promoter in the process of breast carcinogenesis. However, this work was not supported by detailed examination of rates within single countries by similar analysis [91].

Sandler and co-workers showed that women whose spouses smoked had twice the risk of developing breast cancer as those whose husbands were non-smokers [54], the risk being higher for premenopausal women, and for those with at least a high school education; the odds ratio in the latter group increased to 9.0 after adjustment for active smoking [92]. Hirayama found that women married to smokers of one or more packs per day have an overall RR of breast cancer of 1.73 as compared to those married to non-smokers ($P = 0.018$). When analysed by age groups of wives or standardised by occupations of husbands, the risk for breast cancer revealed a significant dose–response relationship: at age 50–59 years when husbands smoked 1–19 and 20 or more cigarettes daily, the RR for mortality from breast cancer were 1.3 and 2.68, respectively ($P = 0.009$); this effect was independent of each of the other risk factors, such as number of children [93].

*Brain tumours* (*Table* 4)

Hirayama found significantly increased mortality among the ETS-exposed wives, although no stratification by tumour type was reported [87].

The Adelaide Brain Tumour Study provided data on ETS exposure for 110 glioma subjects, 60 meningioma subjects and 417 controls [94]. No association of glioma with passive smoking was found. However, increased risk for meningioma associated with active smoking and even higher risks in those exposed to ETS from their spouse were observed, especially among females.

*Colorectal cancer* (*Table* 4)

Colorectal cancer incidence rates were compared in a 12-year prospective study of 25 369 women and 22 973 men, recruited in Washington County, Maryland, U.S.A. [95]. According to the authors, the conclusions about ETS exposure should be regarded with caution: whereas ETS-exposed women demonstrated a decreased risk as compared to those unexposed, men who lived with smokers had increased RR. As these results were found to be consistent with the hypothesis that colorectal cancer may be mediated in women by oestrogens and other steroid

*Table 4. Summary of studies on ETS exposure and non-active smoking-related cancers*

| Author (year, country) | Never smoked patients | Type of cancer | Results | | | | | Reference |
|---|---|---|---|---|---|---|---|---|
| Hirayama (1984, 1992 Japan) | 91 540 wives | | RR (90% C.I.) according to husband's smoking habit | | | | | [87, 93] |
| | | | NS | ES | 1–14 | 15–19 | ⩾ 20 | |
| | | Nasal sinus ($n$ = 28) | 1.00 | — | 1.67 | 2.02 | 2.55 | |
| | | | | | 0.67–4.2 | 0.64–6.33 | 1.04–6.27 | |
| | | Brain ($n$ = 34) | 1.00 | — | 3.03 | 6.25 | 4.32 | |
| | | | | | 1.07–8.58 | 2.01–19.4 | 1.53–12.1 | |
| | | Stomach ($n$ = 854) | 1.00 | 1.15 | 1.00 | 1.00 | 1.01 | |
| | | | | 0.93–1.43 | 0.86–1.17 | 0.81–1.22 | 0.86–1.19 | |
| | | Breast ($n$ = 115) | — | — | — | — | 1.73 | |
| | | | | | | | 1.12–2.66 | |
| Fukuda and Shibata (1990, Japan) | 35 | Nasal sinus | RR according to the number of smokers | | | | | [88] |
| | | | 0 | 1.00 | | | | |
| | | | 1 | 1.40 | | | | |
| | | | > | 5.73 | $P < 0.05$ | | | |
| Sandler *et al.* (1985, U.S.A.) | 32 | Breast | RR | (95% C.I.) | | | | [54] |
| | | | 2.0 | (0.9–4.3) | | | | |
| Ryan *et al.* (1992, Australia) | NA | Brain | | Glioma | Meningioma | | | [94] |
| | | | Both sexes | RR (95% C.I.) | RR (95% C.I.) | | | |
| | | | Ever exposed | 1.24 (0.7–2.0) | 1.91 (1.0–3.6) | | | |
| | | | Never smoked | 1.30 (0.6–2.7) | 2.45 (0.98–6.1) | | | |
| | | | Females | | | | | |
| | | | Ever exposed | 1.41 (0.6–2.8) | 2.71 (1.2–6.1) | | | |
| | | | Never smoked | 1.14 (0.5–2.5) | 2.54 (0.9–6.8) | | | |
| | | | Males | | | | | |
| | | | Ever exposed | 1.06 (0.5–2.1) | 0.95 (0.84–1.06) | | | |
| | | | Never smoked | 2.01 (0.4–9.0) | 2.85 (0.2–33.7) | | | |
| Sandler *et al.* (1988, U.S.A.) | 25 369 women 22 973 men | Colon, rectum | | Age adjusted RR | | | | [95] |
| | | | | PS | Smokers | | | |
| | | | Women | 0.74 (0.56–0.97) | 0.76 (0.52–1.10) | | | |
| | | | Men | 2.99 (1.77–5.04) | 1.42 (0.91–2.22) | | | |

RR, relative risk; C.I., confidence interval; NS, non-smoker; ES, ex-smoker; NA, not available; PS, passive smoker.

hormones, the increased RR for male passive smokers is especially difficult to explain.

*Endocrine tumours*

As part of their case–control study, Sandler and colleagues observed a significant risk (RR 4.4; 95% C.I. 1.2–17.4) of endocrine tumours among exposed non-smokers [54]. However, this result was based on 13 cases.

*All sites combined*

The studies showing results for all cancer sites combined are summarised in Table 5. Hirayama observed a significant elevation of risk for cancer of all sites, and noted a dose–response relationship with the amount of the husband's tobacco consumption [87]. However, this risk elevation was limited to cancers of the lung, nasal sinuses, brain and breast (Table 4), while no significant associations were observed with other cancers such as those of the mouth, pharynx, oesophagus, stomach, colon, rectum, liver, pancreas, peritoneum, cervix, ovary, urinary bladder, skin, bone, malignant lymphoma or leukaemia.

Sandler and co-workers [54] examined the overall cancer risk from adult passive smoking in a case–control study, including 518 cancer cases in North Carolina. Cases included all sites except basal cell cancer of the skin, and were between the ages of 15 and 59 years at the time of diagnosis. Overall cancer risk among individuals ever married to smokers was 1.6 times that of those never married to smokers ($P < 0.01$). RR increased to 2.1 ($P < 0.01$) in lifelong non-smokers, after adjustment for age, race and sex. However, the risk from ETS exposure was statistically significant only among females, and among individuals between the ages of 30 and 49 years.

Gillis and Hole assessed the risk of mortality in non-smokers enrolled in a prospective cohort study carried out in an urban west Scotland population whose members are homogeneous by social class and ethnic group [34, 35]. Total mortality was higher among passive smokers than controls. This was reflected in the category of all causes of death related to smoking. However, no information was available concerning mortality from cancer other than lung cancer.

Sandler and colleagues evaluated mortality associated with ETS exposure in a 12-year study of 27 891 white, adult, smokers and 19 035 never smokers identified in 1963, in Washington County, Maryland, U.S.A. [96]. The adjusted RR of death from all causes were 1.17 (95% C.I. 1.01–1.36) for men, and 1.15 (95% C.I. 1.06–1.24) for women. Overall cancer risk was increased only among women younger than age 50. However, very limited information was available on cancer mortality.

Miller conducted a retrospective study examining the cancer mortality of non-smoking wives with no known or minimal ETS exposure in contrast to non-smoking wives with moderate to

*Table 5. Summary of studies on ETS exposure and deaths from all cancer sites combined*

| Author (year, country) | Population | Results | Reference |
|---|---|---|---|
| Hirayama (1984, Japan) | 91 540 NSM wives; 1309 cancers all sites | RR (90% C.I.) according to husband's smoking habit: NSM 1.00; ETS —; 1–14 —; 15–19 —; ⩾ 20 1.23 (1.12–1.35) | [87] |
| Sandler *et al.* (1985, U.S.A.) | 231 NSM cancers all sites | RR (95% C.I.) from ETS exposure from the spouse: 2.1 (1.4–3.0) | [54] |
| Hole *et al.* (1989, Scotland) | 1538 NSM | Age-standardised mortality/10 000/year for women: Controls; Low ETS 58.3; High ETS 64.6; 35 87.8<br>All causes<br>Smoke-related deaths 34.9 35.2 47.3 | |
| Sandler *et al.* (1989, U.S.A.) | 9551 women 1248 men, never smokers, ETS-exposed; 12 years follow up | RR (95% C.I.) of death from cancer among never smoking, ETS-exposed, subjects:<br>All sites: Men 1.01 (0.66–1.53); Women 1.00 (0.82–1.21)<br>Smoke-related: Men 0.96 (0.43–2.16); Women 1.45 (0.88–2.40)<br>Other: Men 1.03 (0.40–2.62); Women 0.93 (0.76–1.54) | [96] |
| Miller (1990, U.S.A.) | 906 deceased NSM women | Number of deaths: Expected / Observed / *P*<br>All cancers<br>Non-exposed 24.0 / 4 / 0.00002<br>Exposed non-employed 73.1 / 78 / NS<br>Exposed employed 70.6 / 108 / 0.001<br>Digestive cancer<br>Non-exposed 9.3 / 1 / 0.002<br>Exposed non-employed 24.2 / 28 / NS<br>Exposed employed 20.4 / 38 / 0.01<br>Passive smoking-associated cancer<br>Non-exposed 9.2 / 0 / 0.0002<br>Exposed non-employed 35.7 / 34 / NS<br>Exposed employed 38.9 / 54 / NS | [74] |

RR, relative risk; CI., confidence interval; NSM, never smoked; NS, not significant.

lifetime ETS exposure, in the household and in the workplace, in Erie County, Pennsylvania, U.S.A. [74]. The major finding from this study was that ETS-exposed women had a higher probability of dying of cancer of all sites than women who had no known exposure, i.e. cancer mortality in non-smoking wives with no known exposure was very low—only 2.2 vs. 25.5% for exposed women and 35.3% for wives who smoked. Only four cancer deaths (one from digestive cancer, and three from other cancers) were observed in the unexposed group whereas 24 were expected. In particular, there were no reported deaths from lung cancer, breast cancer, genitourinary or lymphatic cancer in that group.

## CHANCE, BIAS AND CONFOUNDING FACTORS

It is very unlikely that chance alone might explain the association between ETS and lung cancer: even if the increase in risk is not likely to be higher than 40%, the size of the populations which have been studied is large enough to exclude with reasonable confidence the possibility that it originated only by random statistical variation: overall, 3453 lifelong non-smoking lung cancer cases have been included in the published studies, 2716 of them (79%) after the 1986 reports which already concluded on the carcinogenic role of ETS. On the other hand, considering that the association between ETS exposure and cancers in adults other than lung cancer, if existing, is presumably weak, one must wonder whether chance alone could explain the reported findings. In addition, most of the studies which we have reviewed, especially the initial ones, although sometimes suggestive of a positive effect, have had several deficiencies which can substantially bias study results, increasing the difficulty in their interpretation, especially if the likely effect of ETS is small [97, 98]. Finally, unrecognised confounding factors may have produced spuriously positive results.

Of particular concern as a possible source of bias, especially for smoking-related cancers, are former and current smokers who report themselves as non-smokers and, thus, may have been at higher risk than true non-smokers, because of a history of smoking and not because of exposure to ETS. Hence, a health effect from active smoking may be contaminating, and falsely elevating, the evaluation of the risk of ETS, if this misclassifi-

cation is more often among cases than controls. Of particular concern is the recognised concordance of smoking habits in married couples [99–102]: a woman who claims to be a non-smoker is more likely to be or to have been an actual smoker if married to a smoker than if married to a non-smoker. In comparison, misreporting among controls—and unrecognised exposure due to background ETS—tends to overestimate the percentage classified as exposed to ETS. This artificially elevates the proportion of exposed controls relative to cases, and contributes to underestimation of risk. Therefore, there may be additional sites for which the relationship to smoking has been obscured. A better reference category for these studies may be a truly unexposed comparison group. Using breast cancer as an example, Wells assumed that the odds ratios could, therefore, be raised from a non-significant level to a significant one [103].

Available data suggest that misclassification of smoking status is not likely to explain the excess risk. The NRC report [21], following the construct of Wald and colleagues [30], assumed that up to 5% of ever smokers are misclassified as never smokers. Fontham and co-workers found that 0.8% of cases of lung cancer, 2.6% of colon cases and 2% of population controls had very high cotinine levels, suggesting that they were actually current smokers [66]. IARC conducted a study explicitly designed to elucidate this methodological issue [104], and found that no more than 2–3% of self-reported "non-smokers" were actually likely to be smokers. Slattery and colleagues [86] validated the non-smoking status of their cases by determining serum cotinine level. They found that, among 94 reported non-smokers, only 4 (4.25%) had levels of serum cotinine above 15 ng/ml, confirming an excellent agreement with the self-reported smoking status.

Very little data are available on the possible confounding effects of other risk factors. Diet (including alcohol intake) [105, 106] may be an important confounder in studies of ETS and cancer [107]. Smokers have been shown to follow a diet which is rich in fat, and poor in vegetables and fruits [108, 109]. If non-smokers who live with smokers are to share similar dietary habits [108, 110, 111], their risk of some kinds of cancer (in particular, lung [112, 113] and breast cancers) could be increased by diet alone. Limited data are available to address this issue. A study from Hawaii, which examined the relationship of ETS to diet for 82 female non-smokers selected among population controls, estimated that the confounding effect of the dietary factors with respect to ETS exposure would not be great [114].

Educational level, occupation [115] and social class have also to be taken into account. For example, the observation by Miller [74] that the non-smoking employed wives had an odds ratio of 2.2 of dying of cancer when compared with exposed non-employed wives, suggests that workplace exposure may involve important hazards in addition to tobacco smoke. Finally, reproductive factors and sexual behaviour of both the subject and spouse may co-vary with the habit of both spouses and have to be taken into account when studying hormone-related cancers.

Statistical considerations must be taken into account: by convention, a probability value less than 5% is deemed statistically significant. However, the $P$ value is a measure of the probability that the finding is due to chance, and it reflects the size of the sample studied. Thus, the absence of statistical significance for an association between an exposure and a disease may not necessarily be indicative of the absence of causality [116], but may reflect an inadequate sample size [16]. Studies of the concentrations of cotinine in the urine and saliva of passive smokers suggest that the dose received may be equivalent to smoking up to three cigarettes a day [117]. Though the same dose received passively may not translate directly to the same risk as in active smokers, it is conceivable that the risks expected for passive smokers may be of a similar magnitude to those found in light active smokers. Consequently, only very large studies would have sufficient power to detect such risks. An alternative way to interpret the results of studies with inadequate power is to merge them in some kind of meta-analysis. However, excluding the association of ETS and lung cancer, the usefulness of such an approach is at least questionable when most of the studies either have different designs or suffer from methodological deficiencies [78, 118, 119], as in this case of the studies reviewed above. Therefore, this approach has not been followed here.

## CRITERIA FOR A CAUSAL ASSOCIATION

The criteria to consider, in judging whether an association observed between a particular factor and disease is one of cause and effect, have been extensively discussed [120, 121]. All the available data seem to fulfill, at the present time, and at least to reasonable degree, the criteria needed to accept a causal link between ETS and lung cancer among lifelong non-smokers [122].

The problem is much more complicated when dealing with ETS and cancers other than the lung. A dose–response relationship has not been considered in the majority of the studies. Few studies attempted to characterise exposure more specifically than using the numbers of smokers at home. Sandler and co-workers found that the risk of all cancers increased with cumulative lifetime exposure to household members who smoke [123]. Recent studies [63] suggest that smoking by spouses contributes a large proportion of lifetime exposure to ETS but that other sources can be important contributors. Thus, the fact that many studies took into account only the spouse's smoking status can partially explain the negativity of the findings. However, while smoking by a spouse may only roughly reflect the amount of tobacco smoke exposure, it appears to distinguish the most exposed from the least exposed [124–126]. Overall, the available evidence is sparse for most cancer sites; however, the two available studies on the urinary bladder are negative, and the two available studies on sinonasal cancer are positive with a strong dose–response relationship. Moreover, there are two positive studies on cervical cancer, one of which suggested a dose–response relationship, and two positive studies on breast cancer. The facts that RR of cervical cancer were as high as those found for active smoking, and that active smoking is not a recognised risk factor for breast cancer, argue against the presence of a causal association.

Biological plausibility must especially be questioned. Combustion of tobacco products indoors contaminates air with nearly 5000 chemicals [2]. Obviously, sidestream smoke is diluted in a considerably large volume of air, which reduces the concentrations inhaled by the involuntary smoker in comparison to those inhaled by the active smoker. Nevertheless, involuntary smoking is accompanied by exposure to many of the toxic agents generated by tobacco combustion; furthermore, the intake of tobacco smoke components—including the carcinogens [12] and mutagens [127, 128]—by non-smokers has been confirmed by studies using biological markers such as cotinine [125, 129–132].

In particular, the results of elevated risk of sinonasal cancer [87]—in addition to the risk of lung cancer—strengthen the plausibility of carcinogenic hazards of sidestream smoke inhalation through the nose. Hence, during passive smoking, most people breathe the mixture of sidestream and exhaled main-

stream smoke through the nose [24]. Thus, if there were to be a carcinogenic effect of ETS exposure, the prime site of action might be the nasal airway rather than the bronchi.

When found, the association between ETS exposure and cancers not related to active smoking is difficult to interpret, and necessarily regarded with caution. We may be seeing the effect of unrecognised confounder(s). On the other hand, other possible mechanisms may be involved. A hypothesis is that the carcinogenic tar being contained mostly in the vapour phase of ETS (which is inhaled through the nasal passages) could result in doses deep in the lung [76, 133, 134], being more easily absorbed into blood and lymph, and distributed to fatty tissue, including the breast [135], whereas tar, contained in directly inhaled smoke, may be primarily deposited in the mouth and larger airways of the lung [136]. Another report showing that enzyme activity can be induced by ETS exposure strongly suggests that components of cigarette smoke enters the bloodstream and are circulated throughout the body of the passive smoker [137]. Therefore, if the studied tumour is more closely associated with carcinogens in the vapour phase, then passive smoking could constitute a more important exposure than direct smoking.

## RISK ASSESSMENT

The individual risk of non-neoplastic respiratory diseases 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 is still a matter of research and debate.

The proportion of lung cancer cases among non-smokers that could be attributed to ETS has been estimated to be, in western countries, about 20–30% [138]. Estimates are available on the number of lung cancer cases caused by ETS exposure in Canada [139], Australia [140], New Zealand [141], U.S.A. [21, 142–144] and England [145]. As an example, the U.S.A. EPA Report recently gave an estimate of 3060 annual lung cancer deaths, in U.S.A., non-smokers aged 35 and over, attributable to ETS. Wells [76] estimated that 46 000 annual deaths occur due to ETS exposure in the U.S.A., consisting of heart disease (32 000), lung cancer (3000) and other cancers (11 000); however, the author did not provide details on the sites involved.

As medical evidence on the harmful effects of ETS has accumulated since the early 1970s, there has been a parallel increase in legal action [76, 146–151]. Many non-smokers and public associations are arguing for the rights of non-smokers to avoid the potentially harmful effects of ETS [152]. Following the example of France, which has recently promoted a law prohibiting advertising and restricting smoking at work and in public places to designated areas, one can support a common action of the European Community to protect the non-smokers.

## CONCLUSION

The ubiquitous presence of tobacco smoke in homes, workplaces, public and private areas has made, until recently, exposure to ETS virtually unavoidable [124]. Involuntary exposure to tobacco smoke has only been intensively investigated as a risk factor for disease in non-smokers in the past decade. Consequently, the evidence on ETS is more limited in scope than for active smoking, and controversy remains concerning the association of ETS with certain diseases [27]. Although ETS-related lung carcinogenesis can be considered as definitely established [23, 80], there is, as yet, no final evidence of an association between ETS exposure and cancer at sites other than the lung. However, such a conclusion is still based on limited information, and considering the large number of studies which have resulted in widely divergent findings, methodologically improved studies with larger sample sizes are needed [22, 24, 74]. There are sites such as the nasal cavity and the sinuses for which the available evidence strongly suggests the presence of an effect, while for other sites, such as the urinary bladder, it rather suggests the absence of an association. The suggestion of an effect on other sites, such as the uterine cervix, the brain and the breast is more difficult to interpret. Yet, full resolution would seem unnecessary for the evolution of public policy on ETS, an air pollutant with a readily controllable source. Our priority must be to continually encourage the reduction in tobacco use [153].


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# News

## Cytogenetics and Molecular Genetics of Human Solid Tumours

The Fourth European Workshop on Cytogenetics and Molecular Genetics of Human Solid Tumours will be held in Amsterdam between 23–26 April 1994. The workshop will bring together all European groups working in the field of solid tumour genetics, including clinicians and pathologists, and the programme will include sessions on specific genetic mechanisms in tumorigenesis, technical developments in genetic analysis of human solid tumours, and particular types of tumours. For more information please contact Mrs J.M. van Dam, 4th European Workshop on Cytogenetics and Molecular Genetics of Human Solid Tumours, Congress Office - Bureau PAOG-Amsterdam, Tafelbergweg 25, 1105 BC Amsterdam, The Netherlands. Tel: (31) 20 566 4801, Fax: (31) 20 696 3228.

## Thirteenth International Papillomavirus Conference

The Thirteenth International Papillomavirus Conference will be held in Amsterdam between 8–12 October 1994. Wide ranging topics will be addressed including cell transformation, viral gene expression, transcriptional control, pathogenesis (mucosal and cutaneous viral infections), immunity and diagnosis. For more information please contact Mrs Carla Schoof, Conference Secretariat, Bureau PAOG Amsterdam, Tafelbergweg 25, 1105 BC Amsterdam, The Netherlands. Tel: (31) 20 566 4801, Fax: (31) 20 696 3228.

## Radiotherapy Technique, Dose and Fractionation in Breast-Conserving Treatment: Current Issues

The British Institute of Radiology has organised the above meeting, which will be held on 29 October 1993. Invited speakers will include Dr J. Yarnold (London), Dr G. Ribiero, (Manchester) and Mr M. Dixon (Edinburgh). For further information please contact Miss Charlotte McLeish, BIR, Conference Office, 36 Portland Place, London W1N 4AT, U.K. Tel: 071 436 7807, Fax: 071 255 3209.

## Monitoring of the Intra-Tumour Environment and Its Relationship to Therapy

The British Institute of Radiology has organised the above meeting, which will be held on 12 November 1993, and invited speakers will include Professor P. Vaupel (University of Mainz), Professor J. Griffiths (St George's Hospital, London), Dr P. Price (Hammersmith Hospital, London) and Dr N. Rowell (Oxford). For further information please contact Miss Charlotte McLeish, BIR, Conference Office, 36 Portland Place, London W1N 4AT, U.K. Tel: 071 436 7807, Fax: 071 255 3209.