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Environmental tobacco smoke and lung cancer mortality in the American Cancer Society's Cancer Prevention Study II

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Environmental tobacco smoke (ETS) has been classified as a human lung carcinogen by the United States Environmental Protection Agency (EPA), based both on the chemical similarity of sidestream and mainstream smoke and on slightly higher lung cancer risk in never-smokers whose spouses smoke compared with those married to nonsmokers. We evaluated the relation between ETS and lung cancer prospectively in the US, among 114,286 female and 19,549 male never-smokers, married to smokers, compared with about 77,000 female and 77,000 male never-smokers whose spouses did not smoke. Multivariate analyses, based on 247 lung cancer deaths, controlled for age, race, diet, and occupation. Dose-response analyses were restricted to 92,222 women whose husbands provided complete information on cigarette smoking and date of marriage. Lung cancer death rates, adjusted for other factors, were 20 percent higher among women whose husbands ever smoked during the current marriage than among those married to never-smokers (relative risk [RR] = 1.2, 95 percent confidence interval [CI] = 0.8-1.6). For never-smoking men whose wives smoked, the RR was 1.1 (CI = 0.6-1.8). Risk among women was similar or higher when the husband continued to smoke (RR = 1.2, CI = 0.8-1.8), or smoked 40 or more cigarettes per day (RR = 1.9, CI = 1.0-3.6), but did not increase with years of marriage to a smoker. Most CIs included the null. Although generally not statistically significant, these results agree with the EPA summary estimate that spousal smoking increases lung cancer risk by about 20 percent in never-smoking women. Even large prospective studies have limited statistical power to measure precisely the risk from ETS. *Cancer Causes and Control* 1997, 8, 57-64

Key words: Lung cancer, environmental tobacco smoke, nonsmokers, United States.

Introduction

Environmental tobacco smoke (ETS) is a common air pollutant to which many people are exposed. The United States Environmental Protection Agency (EPA) has classified ETS as a known (Group A) human lung carcinogen,[1] based on the numerous carcinogens found in both ETS and mainstream tobacco smoke[2] and on the higher lung cancer risk seen in never-smokers married to smokers in 24 of 30 published epidemiologic studies.[1] From its pooled analysis of 11 published US studies, the EPA estimated that never-smoking women married to smokers had 19

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percent higher lung-cancer risk than did those married to never-smokers (relative risk [RR] = 1.19, 90 percent confidence interval = 1.04-1.35). Because of the ubiquity of ETS exposure, this corresponds to approximately 3,000 lung cancers caused annually by ETS among US never-smokers and former smokers, in addition to other adverse effects on respiratory infections and asthma from ETS in children.[1]

Epidemiologic studies of ETS cannot make precise measurements of RRs in the range of 1.2 for three reasons. First, lifelong exposure to common environmental pollutants such as ETS is extremely difficult to measure precisely, and misclassification of exposure may bias studies towards the null. Second, potential confounding by active cigarette smoking is so strong that the ETS association can only be evaluated among lifelong never-smokers. Third, the low background incidence of lung cancer in lifelong never-smokers severely limits the statistical power of even large epidemiologic studies, particularly prospective studies. The two published prospective studies of lung cancer and ETS in the US included only nine[3] and 153[4] lung cancer deaths among never-smoking women. More than 1,000 expected cases are needed to achieve 80 percent statistical power (1,014 cases assuming RR = 1.2, $\alpha = 0.05$, two-sided testing, and 60 percent of never-smoking women exposed).

Despite these methodologic difficulties, accumulated evidence from diverse prospective and retrospective epidemiologic investigations is an important component of the empirical basis for public health policy when considered in aggregate and in relation to observations from other disciplines.[1] The prospective analyses presented here, although limited in statistical power (247 lung cancer deaths among 288,000 married, never-smoking adults), contribute to this total pool of scientific information.

Materials and methods

Study population

Lifelong nonsmokers (never-smokers) in the analyses were drawn from among 676,526 women and 508,576 men enrolled in Cancer Prevention Study II (CPS-II) (Table 1).[5-7] Subjects were the friends, neighbors, and relatives of more than 77,000 American Cancer Society (ACS) volunteers in all 50 states, the District of Columbia, and Puerto Rico. Enrollment was restricted to persons age 30 and older from families where at least one participating member was 45 years old or older. Enrollees completed a four-page baseline questionnaire in 1982 that included personal identifiers, demographic characteristics, personal and family history of cancer and other diseases, and various behavioral, environmental, occupational, and dietary exposures.

Subjects' vital status was determined in two ways from the month of enrollment through 31 December 1989. First, the volunteers made personal enquiries in September of 1984, 1986, and 1988 to determine whether their enrollees were alive or dead and to record the date and place of all deaths. Second, automated linkage using the National Death Index (NDI) was used to extend follow-up from August of 1988 through 31 December 1989, to confirm known deaths during the first six years of follow-up, and to identify previously unrecognized deaths among the 21,831 (1.8 percent) people lost to follow-up between 1982 and 1988.[8] Death certificates were obtained for 96.8 percent of people known to have died, and cause of death was classified according to the *International Classification of Diseases, Ninth Revision* (ICD-9).[9]

At completion of mortality follow-up in December 1989, 1,080,689 (91.2 percent) were still living, 101,519 (8.6 percent) had died, and 2,894 (0.2 percent) had follow-up truncated on 1 September 1988 because of insufficient data for NDI linkage. Follow-up beyond 1989 was not included in the present analyses because of concern about increasing misclassification of exposures with the passage of time since the baseline interview.

Endpoints

Deaths from lung cancer were defined as primary carcinomas of the lung, bronchus, or trachea (ICD-9 code 162), coded as the underlying cause from the death certificate.[9] We determined the fraction of these tumors that might be metastatic to the lung rather than primary by comparing death certificates and tumor registry diagnoses for all (29) never-smokers who resided within the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) cancer registries. SEER listed primary lung cancer as the diagnosis for 27 (93.1 percent) of these decedents. For two, the primary site was listed as unknown by SEER. We also reviewed death certificates for 247 never-smokers coded as lung cancer deaths in the spousal cohort. Histologic information was available from 115 certificates. Of these, 80 (70 percent) were classified as adenocarcinomas, the principal cell type seen in other studies of ETS.[10] The histologic information was considered too incomplete to support separate analyses by cell type.

ETS exposure assessment

Information on potential ETS exposure was obtained at baseline only and was not updated during the seven-year follow-up. The CPS-II baseline questionnaire provided two measures of potential exposure. First, active smoking by the current spouse, when combined with age at marriage, reflected potential ETS exposure to cigarettes, pipes, or cigars (from smoking husbands) or cigarettes

only (from wives) during the present marriage. We obtained the information on active smoking directly from the spouse and linked this to the index never-smoker. Spousal smoking was classified by status (never-, ever-, continuing, or former), duration (years of smoking in the current marriage) and intensity (cigarettes per day) at the time of enrollment, and pack-years of potential exposure during the marriage (the product of duration and cigarettes per day). Spousal information provided our only measure of the long-term duration of exposure, which in active smokers is the single largest contributor to lung cancer risk.[11,12] Fewer than two percent of subjects were excluded from the analysis because of missing data on spousal smoking (Table 1).

Self-reported information on ETS exposure was elicited by the question, 'Whether or not you smoke, on the average how many hours per day are you exposed to the smoke of others: at home _____, at work _____, in other areas _____?' These questions referred to current rather than past exposures and were often left 'blank.' No information was reported in one, two, or three of the self-reported fields for 18 percent, 30 percent, and 26 percent of women and 15 percent, 26 percent, and 13 percent of men, respectively. To determine whether 'blank' values should be considered unexposed or be excluded, we compared the prevalence of ETS exposure at home in CPS-II and in the 1988 National Health Interview Survey (NHIS).[13] Prevalence in the two surveys was most similar (difference usually less than five percent within gender and race subgroups) when 'blank' ETS values in CPS-II were considered 'zeros.' Our analyses, therefore, combined the hours of ETS exposure in the three settings, considering 'blank' values to indicate no exposure. Self-reported data on ETS exposure were considered less informative than were the spousal reports because of the many 'blank' values and the lack of information on duration.

Exclusions

Table 1 shows the number of subjects and deaths from lung cancer that remained in the spousal and self-reported analytic cohorts after exclusions. All analyses excluded ever-smokers, persons whose smoking was unclassifiable, and those who reported extant cancer (except non-melanoma skin cancer) at enrollment (Table 1). The spousal analyses also excluded persons without a participating spouse, those whose smoking status was unknown, and those whose date of marriage or whose spouse's age of starting or stopping smoking were missing. Analyses of self-reported ETS exposure excluded index subjects for whom hours of exposure were unquantifiable. Exposed women in the dose-response subanalyses of the spousal cohort (not shown in Table 1) were restricted further to 92,222 never-smoking women married only once to men who smoked only cigarettes and who provided complete information on years of smoking, cigarettes smoked per day, year of quitting, and age at marriage.

Analyses

We used Cox proportional hazards (PH) modeling[14] to compare lung cancer death rates in never-smokers with or without ETS exposure. The principal contrast involved exposure to spousal smoking (never- *cf* ever-, continuing, or former). Women were categorized further according

Table 1. Number of Cancer Prevention Study (CPS)-II persons and deaths from lung cancer included in or excluded from the analyses, ACS

	Women		Men	
	Persons	**Deaths**	**Persons**	**Deaths**
Total cohort	676,526	2,686	508,576	5,469
Exclusions:				
Ever smoked	286,869	2,190	365,275	5,173
Smoking unclassified	34,140	95	16,139	137
Lung cancer at baseline	154	38	28	10
Other cancers at baseline	31,172	74	6,012	22
No spouse in CPS-II[a]	103,776	113	15,510	18
Unknown exposure in marriage[a]	17,673	13	3,224	3
Spousal smoking unclassified[a]	10,508	13	5,846	9
Self-reported ETS unclassifiable[b]	42,655	43	10,435	11
Analytic cohorts				
Spousal	192,234	150	96,542	97
Self-reported	281,536	246	110,687	116

[a] Excluded from spousal analyses only.
[b] Excluded from self-reported environmental tobacco smoke (ETS) only.

to the type of tobacco smoked by their husbands (cigarettes only, cigars/pipes only, or mixed), years in marriage to a smoker (1-17, 18-29, 30+), cigarettes per day smoked by the spouse (0, 1-19, 20-39, 40+), and cumulative pack-years of exposure (1-16, 17-35, 36+). Dose-response trends could not be examined in men because of insufficient numbers of deaths.

We also measured multivariate RRs according to the total number of hours of self-reported ETS exposure per day (0, 1-2, 3-5, 6+) reported at enrollment. We compared the lung cancer RR in a subgroup of women who had a smoking spouse and also reported ETS at home (n = 33,030) with the rate among women who had neither (n = 41,817), reasoning that this group would have the least misclassification with respect to current exposure. We also tested the proportional hazards assumption during follow-up using univariate survival curves and displaying the Kaplan Meier estimates in a log-log scale.[14]

Adjustment for confounding

Gender-specific PH analyses controlled either for age only (nine categories) or for: age; race (White *cf* non-White); years of education (< 12, 12+); blue collar employment (most recent or current job); occupational asbestos exposure (yes/no); weekly servings of vegetables or citrus fruit (carrots, squash, corn, green leafy vegetables, cabbage, broccoli, Brussels sprouts, tomatoes, and citrus fruits and juices) (≤ 2, 2-11, 12-15, 16-20, 21+); total dietary fat intake in quintiles;[15] and self-reported history of chronic lung disease (asthma, chronic bronchitis, emphysema, tuberculosis) (yes *cf* no). A trend test for dose-response treated the categories as equally spaced ordinal variables in a Cox PH model.

Statistical power and inference

As mentioned, even very large prospective studies have minimal statistical power (or precision) to measure RRs in the range of 1.2 for uncommon illnesses. The statistical power of the spousal CPS-II analyses was 15 percent in women and 10 percent in men (based on the above assumptions, 150 and 97 observed lung cancer deaths in women and men, and 60 percent and 20 percent of women and men exposed). Despite the imprecision of the RR estimates, we assessed whether the risk patterns were consistent with those of active smoking and lung cancer. We hypothesized that: (i) risk caused by ETS should increase as long as the spouse continued to smoke, but the RR should begin to decrease after cessation; (ii) risk in the never-smoker should increase with indices of cumulative spousal smoking; and (iii) risk should be higher for exposure categories that have the least amount of misclassification (*i.e.*, in persons married to smokers who also report current ETS exposure at home).

Results

Spousal smoking

Fifty-nine percent of never-smoking women in CPS-II were married at baseline to a husband who currently (27.6 percent) or formerly (31.8 percent) smoked during the marriage (Tables 2 and 3). Proportionately fewer never-smoking men were married to current (10.3 percent) or former (10.4 percent) smokers. Women potentially exposed to spousal ETS outnumbered men by nearly six to one, due to more men having been excluded because of active smoking (Table 1) and fewer never-smoking men being married to smokers (Table 2).

Demographic differences between persons exposed and unexposed to ETS in the spousal analyses were small and reflected gender and socioeconomic correlates of smoking (Table 2). Compared with unexposed women, wives whose husbands continued to smoke were somewhat less educated and more likely to be employed in a blue collar job; women whose husbands had quit smoking were older and less educated but otherwise similar. Compared with unexposed men, those whose wives formerly smoked were slightly younger, more likely to be actively employed in a non-blue collar job, and more likely to consume vegetables more frequently and fatty foods less often.

Women had potentially greater exposure to ETS from spousal smoking than did men. The number of cigarettes per day, years of smoking, and cumulative pack-years was approximately one-third larger in husbands who smoked than in wives who smoked.

Table 3 presents age-adjusted death rates and RRs for lung cancer, plus multivariate RRs and 95 percent confidence intervals (CI) adjusted for age, race, education, diet, occupational asbestos exposure, and a history of chronic lung disease. Never-smoking women whose husbands ever smoked during the current marriage had 20 percent higher death rates from lung cancer than did those married to never-smokers (multivariate RR = 1.2, CI = 0.8-1.6) (Table 3). The multivariate RR was similar or higher when the husband continued to smoke (RR = 1.2, CI = 0.8-1.8) or smoked cigars or pipes (RR = 1.5, CI = 0.8-2.9). For never-smoking men whose wives smoked, the RR was 1.1 (CI = 0.6-1.8), although this estimate was based on only eight lung cancer deaths. None of the CIs excluded the null (Table 3).

Dose-response spousal subcohort

Compared with never-smoking women whose husbands did not smoke during the marriage, the lung cancer risk among never-smoking women married to cigarette smokers increased with cigarettes per day and with pack-years of spousal smoking but not with years in marriage to a smoker (Table 4). Women whose husbands smoked 40 or more cigarettes per day had the highest risk (RR = 1.9,

Table 2. Demographic characteristics of lifelong never-smokers in spousal cohort, ACS

	Women (*n* = 192,234)		Men (*n* = 96,542)	
	Ever-smoking spouse	Never-smoking spouse	Ever-smoking spouse	Never-smoking spouse
People (no.)	114,286	77,948	19,549	76,993
People (%)	59.5	40.5	20.2	79.8
Age (mean yrs)	55.1	54.2	56.1	57.2
White (%)	95.4	95.2	94.5	95.0
Blue collar worker (%)	8.4	7.1	21.3	28.0
Education				
(% < 12 yrs)	11.1	8.7	9.1	12.2
Dietary vegetables (%)[a]				
1 (least)	3.9	3.2	4.4	4.2
2	20.3	18.4	24.9	24.9
3	19.6	19.0	21.2	21.0
4	23.8	24.5	22.6	23.3
5 (most)	24.0	26.8	20.5	20.4
Dietary fat (%)[b]				
1 (least)	13.9	13.3	12.5	10.9
2	20.5	20.0	17.7	15.6
3	20.9	20.8	18.0	17.4
4	19.5	20.4	20.2	21.0
5 (most)	16.8	17.4	25.2	28.9
Incomplete nutrition data	8.4	8.1	6.4	6.2

[a] Vegetable consumption categories defined as < 2, 2-11, 12-15, 16-20, 21+ servings per week.
[b] Fat consumption index defined by quintiles estimated from fat content of 18 foods, average portion size for age and gender, and frequency of consumption.[12]

Table 3. Lung cancer death rates among married lifelong never-smokers in CPS-II according to smoking by the spouse, ACS

Spousal smoking habits	No. of people	No. of lung cancer deaths	Age-adjusted rate ratio[a]	Multivariate rate ratios[b]	(CI)[c]
Women					
Never smoked	77,948	54	1.0	1.0	—
Ever smoked	114,286	96	1.2	1.2	(0.8-1.6)
Continuing smoking					
Any type	53,139	44	1.3	1.2	(0.8-1.8)
Cigarette only	33,371	26	1.3	1.2	(0.8-2.0)
Cigar/pipe only	9,794	11	1.5	1.5	(0.8-2.9)
Mixed	9,974	7	1.0	1.0	(0.5-2.2)
Former smoking					
Any type	61,147	52	1.1	1.1	(0.8-1.6)
Cigarette only	43,563	39	1.2	1.2	(0.8-1.8)
Cigar/pipe only	6,810	7	1.3	1.3	(0.6-2.8)
Mixed	10,774	6	0.7	0.7	(0.3-1.7)
Men					
Never smoked	76,993	79	1.0	1.0	—
Ever smoked	19,549	18	1.0	1.1	(0.6-1.8)
Continuing cigarettes	9,492	8	1.0	1.0	(0.5-2.0)
Former cigarettes	10,057	10	1.1	1.1	(0.6-2.2)

[a] From Cox PH model adjusted only for age.
[b] From Cox PH model adjusted for age, race, education, dietary consumption of vegetables, and total fat, asbestos exposure, blue collar employment, and history of chronic lung disease.
[c] CI = 95% confidence interval.

Table 4. Number of lung cancer deaths, person-years (PY) at risk, and rate ratios (RR) with 95 percent confidence intervals (CI) among never-smoking women according to various indices of spousal smoking, ACS

	No. of women	Lung cancers	PY	RR[b]	(CI)
Cigarettes per day by spouse[a]					
0	46,149	30	333,946	1.0	—
1-19	11,467	9	83,074	1.1	0.5-2.2
20-39	24,735	22	179,751	1.2	0.7-2.2
40+	9,871	13	71,618	1.9	1.0-3.6
					Trend[b] $P = 0.03$
Years in marriage to smoker[a]					
0	46,149	30	344,946	1.0	—
1-17	14,794	13	107,681	1.5	0.8-2.9
18-29	15,491	14	112,761	1.5	0.8-2.8
30+	15,788	17	114,002	1.1	0.6-2.1
					Trend[b] $P = 0.5$
Pack-years of exposure[a]					
0	46,149	30	334,946	1.0	—
1-16	15,451	10	112,318	1.0	0.5-2.1
17-35	15,569	16	113,119	1.5	0.8-2.7
36+	15,053	18	109,006	1.5	0.8-2.6
					Trend[b] $P = 0.1$

[a] The referent group includes never-smoking women married to husbands who did not smoke during the marriage. The exposed categories are split into approximate tertiles, and are restricted to never-smokers married to cigarette smokers with complete smoking data, married only once, and with valid information on age at marriage.

[b] From a Cox PH model adjusted for age, race, education, dietary consumption of vegetables and total fat, asbestos exposure, blue collar employment, and history of chronic lung disease.

CI = 1.0-3.6, *P* trend = 0.03). Restricting the dose-response analysis to women whose current husbands continued to smoke in 1982 reduced the number of lung cancer deaths and the trend. With this restriction, women whose husbands smoked 20 to 39 cigarettes per day experienced 10 lung cancer deaths, (RR = 1.6, CI = 0.8-3.3); those whose husbands smoked 40+ cigarettes per day had two lung cancer deaths (RR = 0.9, CI = 0.2-4.0, *P* trend = 0.3). Dose-response trends could not be examined in the men because of a statistically insufficient number of lung cancer deaths.

Other analyses

The association between lung cancer and spousal smoking was not stronger among women whose husbands currently smoked and who also reported ETS exposure at home (RR = 1.2, CI = 0.7-2.2). This was based on only 23 exposed cases and had limited precision. The corresponding RRs among men with concordant exposure data could not be examined (two exposed cases).

None of the self-reported current ETS exposure measures (any exposure or total hours of exposure) was associated with increased lung cancer risk. Multivariate RRs among women who reported 0, 1-2, 3-5, or 6+ hours of ETS per day in all settings were 1.0, 0.8, 0.7, and 1.1 based on 175, 19, 11, and 31 lung cancers, respectively. Corresponding RRs in men were 1.0, 0.6, 1.0, and 1.3 based on 74, 20, 8, and 14 lung cancer deaths, respectively.

Graphs of the univariate survival curves associated with spousal ETS exposure indicated that the mortality rate ratios were approximately constant during the seven years of follow-up in CPS II. Further, the assumption of proportional hazards did not appear to be violated in any of the Cox models.

Discussion

Our principal finding was that never-smoking women married to husbands who ever smoked during the marriage had 20 percent higher death rates from lung cancer than those married to never-smokers. Risk was similar or increased when the husbands continued to smoke, smoked more cigarettes per day, or exceeded 35 pack-years of cigarettes during the marriage. Although only one dose-response trend was statistically significant, the magnitude and direction of risk were similar to the pooled value from other US studies,[1] and paralleled temporal patterns seen with active smoking, risk increasing with sustained cumulative (pack-years) of exposure and the RR decreasing with cessation.

These results should be interpreted in the context of three lines of evidence cited by the EPA and other scientific groups as support for the carcinogenicity of ETS.[1-2,16-17] First, most of the 3,800 chemicals found in mainstream tobacco smoke (MS) also occur in sidestream smoke (SS). ETS contains both SS and exhaled MS. At

least 42 chemicals identified in MS and SS are known to cause cancer in experimental animals and/or humans.[2] MS accounts for 87 percent of lung cancer in the general population. No threshold is seen in the dose-response relation between active smoking and lung cancer; extrapolation of risk from active smokers to ETS predicts risk estimates in the rage of an RR between 1.03 and 1.36.[18]

Second, biologic markers of inhaled tobacco smoke show that never-smokers exposed to ETS absorb and metabolize measurable amounts of tobacco smoke.[1,2,16,17] Average concentrations of nicotine and its metabolite cotinine in ETS-exposed urban never-smokers are about 0.1-1.0 percent of those seen in active cigarette smokers, although certain components of tobacco smoke are produced disproportionately in SS.[1] A tobacco-specific lung carcinogen 4-(methylnitrosamino)-1-(3-pyridy)-1-butanone (NNK) also has been measured in the urine of ETS-exposed men[19] and occurs at higher concentrations in sidestream than in mainstream smoke.[16] NNK causes pulmonary adenocarcinoma in rodents and may contribute to the excess of lung adenocarcinomas in ETS-exposed never-smokers.[19-22]

Third, most published epidemiologic studies of ETS find higher lung cancer risk among never-smoking women whose husbands smoke than among those married to never-smokers. The EPA report discussed 30 published studies encompassing more than 3,000 lung cancer cases from eight different countries.[1] Twenty-four (80.0 percent) of these studies found higher risk of lung cancer among wives whose husbands ever smoked; nine were statistically significant. Since the EPA report there have been four additional or expanded US studies,[10,23-25] plus three new studies in China.[26-28] The new US studies, counting CPS-II, add over 1,200 lung cancer cases studied in never-smokers. Their results are generally consistent despite low statistical power and large variations in design, location, and analytic methods in individual studies.

The CPS-II exposure data were much less detailed than in case-control studies designed specifically to examine the ETS hypothesis.[10,23,24] Although information on spousal smoking was our best and only indication of long-term potential ETS exposure, this, too, was imperfect. We lacked information on spousal smoking during previous marriages, smoking by other family members or housemates, proximity to the smoker, changes in the number of cigarettes per day smoked by the spouse, and childhood exposure to ETS. No biologic measurements were obtained to validate absorption of ETS. Our analyses could not integrate potential exposure to a smoking spouse with past or present exposure in other settings. The resultant random misclassification of ETS exposure could bias our results towards the null.

Even large prospective studies such as CPS-II have limited statistical precision (wide confidence intervals) when measuring uncommon diseases in a small fraction of the population. Because only two percent of men and eight percent of women in CPS-II were never-smokers married to currently smoking spouses, we traced 676,526 women for seven years to find 150 lung cancer deaths in the subgroup of interest. By contrast, the largest retrospective study[10] identified 653 incident lung cancers in married, never-smoking women in five US cities with a base population of approximately 18,500,000 women. Most other studies of ETS have fewer cases of lung cancer in never-smoking women than CPS-II. The conclusion of some small studies does not always appropriately reflect their imprecision. For example, a recent hospital-based case-control study of 41 lung cancer cases in never-smoking men (RR = 1.60, CI = 0.67-3.82) and 117 cases in women (RR = 1.08, CI = 0.60-1.94)[25] concluded 'little indication of an association' between ETS and lung cancer, despite the overlap in confidence intervals between the study results and the EPA pooled estimate.[1]

CPS-II avoids several biases that have been hypothesized to weaken retrospective studies.[29-32] Spouses described their smoking habits at baseline, before lung cancer had been diagnosed in their partners. This avoids recall bias (awareness of disease influencing the reporting of ETS) and information bias (deceased cases being described by next-of-kin but controls describing themselves). Since the analysis identified only married couples, no bias was introduced as a result of married and unmarried persons describing ETS exposure differently.[30] Small demographic differences were apparent between persons exposed or unexposed to spousal smoking in CPS-II. Adjusting for age, race, vegetable and total fat consumption, education, occupational exposure to asbestos, and prior lung disease had minimal effect on the association with ETS.

Our results pertain largely to lung cancer among never-smoking women married to smoking men. Too few never-smoking men were married to smokers and insufficient information is available on their ETS exposure outside the home to interpret the data on CPS-II men. Because CPS-II was limited to adults, it also lacks information on adverse ETS-related effects in children such as pneumonia, bronchitis, asthma, and middle ear effusions. Such nonmalignant effects may greatly outnumber lung cancer deaths. EPA estimated that ETS caused approximately 3,000 lung cancer deaths annually among US never-smokers (assuming RR = 1.19) and former smokers, compared with 150,000 to 300,000 cases of bronchitis and pneumonia in infants and children up to 18 months of age, and 200,000 to 1,000,000 children whose asthma would be worsened by ETS.[1]

In summary, our findings contribute to the overall evidence that ETS exposure from smoking spouses may adversely affect lung cancer risk in never-smoking women.

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