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Relation of Breast Cancer with Passive and Active Exposure to Tobacco Smoke

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Studies on passive smoking have consistently shown a tendency toward an increased risk of breast cancer, while studies on active smoking have failed to demonstrate an association. This apparent contradiction may stem from not separating passive smokers from the unexposed when assessing the effect of active smoking. A population-based case-control study was conducted in Geneva, Switzerland, between January 1992 and October 1993 to determine the relation of passive and active smoking to breast cancer when the referent unexposed category consisted of women unexposed to active and passive smoke. The 244 patients with breast cancer (cases) were compared with 1,032 women free of breast cancer (controls). The lifetime history of active and passive smoking was recorded year by year, between the age of 10 years and the date of the interview. The adjusted odds ratios of breast cancer for ever active smokers, compared with women unexposed to either passive or active smoke, were 2.2 (95% confidence interval (CI) 1.0–4.4) for an average lifetime consumption of 1–9 cigarettes per day, 2.7 (95% CI 1.4–5.4) for 10–19 cigarettes per day, and 4.6 (95% CI 2.2–9.7) for 20 or more cigarettes per day. Among passive smokers, the adjusted odds ratio was 3.2 (95% CI 1.6–6.3) for being exposed for the equivalent of 2 hours per day for 25 years. The odds ratios were adjusted for known or postulated risk factors of breast cancer, including alcohol and saturated fat intake. There was no evidence of strong selection, detection, or recall biases. Active and passive exposure to tobacco smoke may increase the risk of breast cancer. Additional studies are needed to decide whether the association is causal. Further elucidation of this relation would benefit not only the prevention of breast cancer but also the prevention of other smoking-related diseases in women. *Am J Epidemiol* 1996;143:918–28.

breast neoplasms; environmental pollution; smoking; tobacco smoke pollution

In the absence of identified preventable risk factors for breast cancer and given the large prevalence of exposure to both active and passive smoking in the female population of most countries, the potential relation of smoking with breast cancer is worth studying with great care. A recent report suggests that active smoking may be a strong risk factor among women who are slow acetylators (1). These women may be highly susceptible to compounds of tobacco smoke that have been shown to be carcinogenic in animals (2, 3).

The relation of active smoking to breast cancer has been investigated in large and well-conducted studies (4–24). Overall, the association has been found to be either weakly positive (7, 9, 11, 13, 15, 17, 20, 22, 23) or absent (5, 6, 8, 12, 14–16, 18, 19, 21, 24). Very few reports suggest that active smoking may confer a protection against breast cancer (4, 10). In contrast, reports on the passive smoking-breast cancer relation are less numerous but more consistent. Two studies (25, 26) have shown that being married to a smoker increased the risk of breast cancer in women who never smoked actively (27). In the United Kingdom national case-control study, the risk of breast cancer was increased in women aged <36 years who had been exposed to passive smoking during childhood and adulthood, but there was no evidence of a dose-response (24).

It is therefore paradoxic that the work on passive smoking has consistently shown a tendency toward an increased risk of breast cancer while studies on active smoking have failed to demonstrate an association. This apparent contradiction may stem from not separating passive smokers from the unexposed when assessing the effect of active smoking. In all previous studies (4–24), the effect of active smoking has been determined relative to never active smokers. This referent category combined women who were passive

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Abbreviations: CI, confidence interval; OR, odds ratio.

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smokers with women unexposed to either active or passive smoke. If passive smokers are at greater risk of breast cancer than are the unexposed, grouping passive smokers with the unexposed in the referent category may reduce the excess risk for active smokers to nonsignificant levels. This was the a priori hypothesis that motivated the design of the present study.

The present population-based case-control study was specifically designed and conducted to determine the relation of active and passive smoking to breast cancer. The methodology had several innovative aspects with respect to previous work. A detailed lifetime history of exposure to active and passive smoking was obtained from all participants. The referent unexposed group consisted of women never regularly exposed to either passive or active smoking. Information was obtained to assess possible selection, detection, or recall biases.

MATERIALS AND METHODS

Case and control selection

Eligible cases were all women aged <75 years who were resident of Geneva, Switzerland, with a first diagnosis of invasive breast cancer between January 1, 1992, and October 31, 1993. All possible sources of breast biopsies in Geneva participated in the study, that is, three private laboratories and the University Hospital Pathology Department. Physicians in charge asked each of their patients whether they agreed to participate and sent a signed consent form to the study coordinators. Afterwards, the same recruitment protocol was followed for cases and controls. Of all the eligible cases reported to the Cancer Register of Canton Geneva during the study period (n = 344), 71 percent were interviewed. Of the noninterviewed cases, five (1.5 percent) had died, 65 (18.8 percent) refused to participate, and 30 (8.7 percent) could not be contacted because of physician refusals. The age distribution of interviewed cases compared with that of eligible cases was almost identical. Pathology reports were obtained for all breast cancer cases.

To qualify as a population control, a woman had to be a resident of Geneva between January 1992 and October 1993 and aged 30–74 years. An age-stratified random sample was selected from an official list of all residents published every year and comprising names, date of birth, address, and nationality. Eligible controls received a first letter, followed if necessary by up to seven telephone calls on different days of the week and at different hours of the day and then by a second and third letter. This standardized recruitment procedure lasted no more than 3 months. Of the eligible controls (n = 1,473), 70 percent were interviewed. The size of the control group represented the maximum number of women who could be interviewed and examined in a mobile unit over the time period during which incident cases were recruited.

Data collection

Cases and controls were invited to come to a mobile clinic and to participate in an ongoing survey on women's health. The aim of the study was not specified, and trained interviewers were blind to the case-control status. Interviews took place 2 days per week in 1992 and 1 day per week in 1993. Participants could choose to come to the more convenient of two possible locations downtown where the mobile clinic was parked.

The overall interview took about 45 minutes, of which about 20 minutes were dedicated to smoking history. Questions covered the major known or postulated risk factors for breast cancer. The smoking history section of the questionnaire was structured as four calendars, one dedicated to active smoking and three separate calendars dedicated to passive exposures at home, at work, and during leisure time. In each calendar, lines corresponded to ages and columns to items that varied according to the type of smoking exposure. Smoking exposures were recorded year by year, between the age of 10 years and the date of the interview. An episode of exposure consisted of a time period of at least 6 months during which the woman had passively or actively smoked. For each episode of exposure, the woman was asked to indicate the age at which she was exposed and the corresponding calendar years. In addition, for each episode of active smoking, the number of cigarettes per day, the presence or not of a filter, and the cigarette brand were recorded. The number of hours per week of each passive smoking episode was recorded.

All women recruited during the second year of the study (n = 486) completed at home a self-administered, semiquantitative food frequency questionnaire. This food frequency questionnaire had been developed and tested in the study target population during the first year of the study and was not available before January 1993 (28–30). It comprised a list of 80 food items and serving sizes that could be converted into daily energy, nutrients, and alcohol intakes (30). All women interviewed in 1993 brought back the food frequency questionnaire on the day of the visit to the mobile clinic, where it was checked by the interviewer.

Information on smoking status was obtained from the women who refused to participate. Controls who refused to participate were asked over the phone by the recruiting persons whether they had ever smoked. For

the cases, this information was reported by the recruiting physician. The proportion of nonparticipants who refused to answer this additional question was less than 1 percent among cases and 2 percent for controls. Agreement between the physician's report of the smoking status of a given case and the answer given by that case in the women's health questionnaire was not available for refusers, but it was 88 percent for those who agreed to participate. Of the nonconcordant cases, 65 percent were exsmokers who had stopped smoking many years before and who had been categorized as nonsmokers by the physician.

Variable definitions

An active smoker had smoked at least 100 cigarettes in her lifetime. Exsmokers had stopped smoking before 1991 if interviewed in 1992 and before 1992 if interviewed in 1993. Variables for active smokers were the average lifetime number of cigarettes per day and the number of pack-years (the average number of packs/day $\times$ the total number of years of smoking). Analyses were repeated for all ever active smokers and separately for current active and ex-active smokers.

Passive smokers were women who reported having been exposed to passive smoke at least 1 hour per day for at least 12 consecutive months during their lifetime. The number of hours per day-years of passive smoking was the sum of "hours/day $\times$ duration" of all episodes of passive exposure at home, at work, or during leisure time. For example, 50 hours per day-years could represent 1 hour per day of passive smoking during 50 years, 2 hours per day during 25 years, or 12.5 hours per day during 4 years.

Self-reported rather than measured weight and height were used to compute the body mass index (weight (kg)/height $(m)^2$). The agreement with measured weight or height available for 53 percent of the study sample was good (intraclass correlation coefficient = 0.96). Education was divided into four categories: elementary school ($\leq$12 years), secondary school (ages 13–18 years), apprenticeship, and having a high school degree (ages 18 and 19 years) or university education. Women without pregnancy (no conception) were categorized separately from women whose pregnancy never ended in a live birth (no birth). Postmenopausal women had had their last menses at least 1 year before the interview or had a bilateral oophorectomy. For cases, the history of breast biopsy comprised biopsies performed at least 6 months before cancer diagnosis.

Statistical methods

The adjusted odds ratios and 95 percent confidence intervals of breast cancer were calculated using unconditional logistic regression (31). Passive smokers were excluded when analyzing the effect of active smoking or, vice versa, active smokers were excluded when analyzing the passive smoking effect.

In the tables, the multivariate odds ratios for each variable are adjusted for all of the following potential confounders: age, education, body mass index, age at menarche, age at first live birth, oral contraceptive use, breast cancer in mother or sister, history of breast biopsy, alcohol intake, and saturated fat intake. Categories are given in table 1. Categories of age were those used in the sampling design of controls as recommended by Breslow and Day (31). When analyses using age as a continuous variable were performed, nearly identical results were obtained. Menopausal status was highly correlated with age and was therefore not treated as a confounder in the models, but analyses stratified by menopause were performed.

Because dietary data were available for the 150 cases and 336 controls who were also a random sample of the target populations of cases and controls, a two-step procedure was used to compute multivariate odds ratios adjusted for fat and alcohol intakes. These are identified in the tables as the "two-step odds ratio" (32, 33). First, multivariate odds ratios were estimated in the small sample (n = 486) with a model including all confounders. In a second step, these estimates and their standard errors were adjusted according to the distribution of passive and active smoking in the large sample (n = 1,276).

Distributions of pack-years in former and current smokers were described by medians and compared using the Wilcoxon test (34). Heterogeneity of proportions was tested using the chi-square test. Tests for trend were obtained by coding the smoking categories as scores with values of 0, 1, and 2 in the multivariate logistic regression model after exclusion of the unexposed category from the analysis (34). These trend tests were not computed for the two-step odds ratios, because these odds ratios were not substantially different from the multivariate odds ratios and because they were not available on standard software programs (32). A logistic regression likelihood ratio test for interaction was used in table 5 to compare the proportions of cases and controls across smoking categories who reported being worried by passive smoking (31, 35).

RESULTS

Characteristics of cases and controls

After the exclusion of 29 controls with a previous history of breast cancer, 244 cases and 1,032 controls were available for analysis. Table 1 compares cases

TABLE 1. Risk factors for breast cancer in 244 cases and 1,032 controls, Geneva, Switzerland, January 1992 to October 1993

Risk factor	Cases*	Controls*	Multivariate† OR‡	95% CI‡
Age (years)				
<40	10	131	1.0	
40–44	16	110	2.1	0.9–5.0
45–49	45	177	3.3	1.6–6.9
50–54	44	138	4.2	2.0–8.9
55–59	46	136	4.4	2.1–9.4
60–64	39	128	4.1	1.9–8.9
65–69	19	99	2.3	1.0–5.6
70–74	25	113	3.0	1.3–6.9
Education				
Elementary	50	226	1.0	
Apprenticeship	46	168	1.2	0.8–1.9
Secondary	69	290	1.1	0.7–1.6
≥High school	77	343	0.9	0.6–1.4
BMI‡ (kg/m^2)				
<21	59	262	1.0	
21–22	62	263	0.9	0.6–1.4
23–25	59	259	0.9	0.6–1.4
≥26	64	243	1.1	0.7–1.6
Age at menarche (years)				
<12	31	129	1.0	
12	49	205	1.1	0.6–1.8
13	73	242	1.4	0.9–2.3
14	50	221	1.0	0.6–1.7
≥15	41	226	0.8	0.4–1.3
Age at first live birth (years)				
<25	62	308	1.0	
25–29	66	247	1.5	1.0–2.2
≥30	42	199	1.2	0.8–1.9
No birth	31	94	1.9	1.2–3 2
No conception	43	183	1.2	0.8–1.9
Oral contraception				
Never	119	455	1.0	
Ever	125	576	0.8	0.6–1.2
Breast cancer in mother or sister				
No	217	981	1.0	
Yes	27	51	2.3	1.4–3.9
History of breast biopsy				
No	204	912	1.0	
Yes	39	120	1.3	0.8–1.9
Alcohol (g/day)§				
None	38	62	1.0	
0.1–5.0	52	133	0.7	0.4–1.3
5.1–10	19	46	0.9	0.4–2.0
>10	41	95	0.6	0.3–1.2
Saturated fat (% of energy intake)§				
≤10	44	83	1.0	
10.1–15	84	185	1.1	0.6–1.8
>15	22	68	0.7	0.3–1.3

* Totals may vary because of missing values.
† The odds ratio for each variable was controlled for all of the other factors in the table but not for active or passive smoking.
‡ OR, odds ratio; CI, confidence interval; BMI, body mass index.
§ For the 150 cases and 336 controls who answered the food frequency questionnaire.

and controls with respect to characteristics reported in the literature to be risk factors for breast cancer. All these variables were kept in the multivariate and two-step models as potential confounders. The ages of controls reflect the age distribution in the general population. Statistically significant differences between cases and controls were found for "no birth" (odds ratio (OR) = 1.9, 95 percent confidence interval (CI) 1.2–3.2) and for the presence of a family history of breast cancer in a mother or sister (OR = 2.3, 95 percent CI 1.4–3.9).

There were 126 cases (52 percent) and 620 controls (60 percent) who were never active smokers. Among them, 28 cases (22 percent) and 241 controls (39 percent) were neither active nor passive smokers and were used as the referent "unexposed" group.

Active smoking

Table 2 shows that the adjusted odds ratios of breast cancer for ever active smokers, compared with women unexposed to either passive or active smoke, were 2.2 (95 percent CI 1.0–4.4) for an average lifetime consumption of 1–9 cigarettes per day, 2.7 (95 percent CI 1.4–5.4) for 10–19 cigarettes per day, and 4.6 (95 percent CI 2.2–9.7) for 20 or more cigarettes per day (test for trend excluding the unexposed, $p = 0.09$). Among current active smokers, the dose-response was even stronger (test for trend excluding the unexposed, $p = 0.007$). The odds ratios also increased with the number of pack-years. Among current active smokers, the odds ratio was 2.1 (95 percent CI 1.0–4.5) for less than 20 pack-years, and it was 2.9 (95 percent CI 1.4–6.0) for 20 or more pack-years. The adjustment for alcohol and saturated fat intakes did not substantially alter the odds ratios.

To examine the effect of cleaning up the referent category from the passive smokers, we computed the odds ratios using never active smokers as the referent category, that is, pooling passive smokers with the unexposed. Among ever active smokers, the two-step odds ratios were 1.2 (95 percent CI 0.8–2.0) for 1–9 cigarettes per day, 1.7 (95 percent CI 1.1–2.5) for 10–19 cigarettes per day, and 1.9 (95 percent CI 1.2–2.9) for ≥20 cigarettes per day (not shown in a table).

Compared with unexposed women, the odds ratios of breast cancer were of a similar magnitude for women who started to smoke actively before (multivariate OR = 3.0, 95 percent CI 1.7–7.0) or after (multivariate OR = 3.5, 95 percent CI 1.7–7.0) their first pregnancy.

Two-step odds ratios of breast cancer among ex-active smokers increased from 3.3 for 1–9 cigarettes per day to 3.7 for ≥20 cigarettes per day, but the trend was not statistically significant (table 2). In each category of cigarettes per day, odds ratios were of a similar magnitude for having stopped for less than 10

TABLE 2. Odds ratio of breast cancer related to active smoking, Geneva, Switzerland, January 1992 to October 1993

Smoking status	Cases*	Controls*	Multivariate†		Two step‡	
			OR§	95% CI§	OR	95% CI
Unexposed to active and passive smoking	28	241	1.0		1.0	
Ever active (cigarettes/day)						
1–9	31	131	2.4	1.3–4.4	2.2	1.0–4.4
10–19	49	163	3.6	2.0–6.2	2.7	1.4–5.4
≥20	38	117	3.7	2.1–6.7	4.6	2.2–9.7
p‖				0.09		
Current active (cigarettes/day)						
1–9	10	78	1.4	0.6–3.2	1.5	0.6–3.9
10–19	26	105	3.0	1.6–5.7	2.1	0.9–4.8
≥20	20	56	4.4	2.1–8.9	5.1	2.1–12.6
p‖				0.007		
Current active (pack-years)						
<20	23	129	2.2	1.2–4.3	2.1	1.0–4.5
≥20	33	110	3.2	1.8–5.9	2.9	1.4–6.0
p‖				0.18		
Ex-active (cigarettes/day)						
1–9	21	53	3.8	1.9–7.5	3.3	1.4–7.6
10–19	23	58	4.5	2.3–8.9	3.6	1.6–8.1
≥20	18	61	3.2	1.6–6.4	3.7	1.5–8.8
p‖				>0.50		

* Totals may vary because of missing values.

† The odds ratios for each variable in the table were adjusted for age, education, body mass index, age at menarche, age at first live birth, oral contraception, breast cancer in mother or sister, and history of breast biopsy.

‡ Also adjusted for saturated fat and alcohol intakes in addition to the factors controlled for in the multivariate analysis.

§ OR, odds ratio; CI, confidence interval.

‖ Test for trend excluding the referent category. All tests for trend using unexposed as the referent group have a p value < 0.05.

years or for 10 years or more (not shown in a table). The total number of pack-years was smaller among ex-active smokers (median pack-years = 9 for controls and 8 for cases) than among current smokers (median pack-years = 18 for controls and 24 for cases). Case-control differences in pack-years were less important among exsmokers (Wilcoxon's p = 0.71) than among current smokers (Wilcoxon's p = 0.048). In addition, among ex-active smokers, cases were much more likely to have a family history of breast cancer (21 percent) than were controls (3 percent).

Passive smoking

Table 3 shows that, among nonactive smokers, the multivariate odds ratio for ever being exposed to passive smoking at home, at work, or during leisure time for at least 1 hour per day for at least 12 consecutive months of smoking was 2.3 (95 percent CI 1.5–3.7). The odds ratio became 3.2 (95 percent CI 1.7–5.9) after additional adjustment for saturated fat and alcohol intakes. There was no statistically significant trend according to the numbers of hours per day-years; the two-step odds ratios were 3.1 (95 percent CI 1.5–6.2) for 1–50 hours per day-years and 3.2 (95 percent CI 1.6–6.3) for more than 50 hours per day-years.

Sources of passive exposure at home were similar for cases and controls; about 60 percent of all episodes were attributed to the husband only, 25 percent to parents only, and 15 percent to other persons or more than one person. The two-step odds ratio for women ever exposed to passive smoke by a spouse compared with women never exposed to passive or active smoke was 3.1 (95 percent CI 1.6–6.1).

Compared with unexposed women, the odds ratios of breast cancer were of similar magnitude for women

TABLE 3. **Odds ratio of breast cancer related to passive smoking at home, at work, or during leisure time, among nonactive smokers, Geneva, Switzerland, January 1992 to October 1993**

Passive smoking status	Cases*	Controls*	Multivariate†, ‡		Two step§	
			OR ‖	95% CI ‖	OR	95% CI
Never passive (<1 hour/day-years)¶	28	241	1.0		1.0	
Ever passive (hours/day-years)						
1–50	44	185	2.2	1.3–3.7	3.1	1.5–6.2
>50	54	191	2.5	1.5–4.2	3.2	1.6–6.3
All	98	379	2.3	1.5–3.7	3.2	1.7–5.9
Ever passively exposed to spouse (hours/day-years)						
1–50	18	71	2.5	1.3–5.0	3.1	1.3–7.5
>50	44	143	2.7	1.5–4.7	3.2	1.5–6.5
All	62	214	2.6	1.6–4.3	3.1	1.6–6.1

* Totals may vary because of missing values.

† The odds ratios for each variable in the table were adjusted for age, education, body mass index, age at menarche, age at first live birth, oral contraception, breast cancer in mother or sister, and history of breast biopsy.

‡ All tests for trend using unexposed as the referent group have a p value < 0.05. None of the tests for trend excluding the referent group has a p value < 0.05.

§ Adjusted for saturated fat and alcohol intakes in addition to the factors controlled for in the multivariate analysis.

‖ OR, odds ratio; CI, confidence interval.

¶ Never exposed to at least 1 hour/day for at least 12 consecutive months during their lifetime.

who started to smoke passively before (multivariate OR = 2.4, 95 percent CI 1.5–3.8) or after (multivariate OR = 2.1, 95 percent CI 1.0–4.2) the first pregnancy.

DISCUSSION

The present results suggest that both passive and active smoking increase breast cancer risk. They seem biologically plausible, since it is reasonable to postulate that constituents of tobacco smoke have a direct and/or an indirect influence on the carcinogenic process leading to breast cancer. The mammary gland is not directly exposed to tobacco smoke, but active smoking is associated with cancers of nonrespiratory organs, such as the bladder or pancreas (36). Several polycyclic aromatic hydrocarbons, including benzo(*a*)pyrene and 7,12-dimethylbenzo(*a*)anthracene, are produced by tobacco combustion and are present in the sidestream smoke of cigarettes (37). Benzo(*a*)pyrene is a well-known human carcinogen (38). 7,12-Dimethylbenzo(*a*)anthracene is used for routine induction of mammary tumors in animals (39). Sprague-Dawley rats exposed to 7,12-dimethylbenzo(*a*)anthracene develop adenocarcinomas having histologic and hormone-dependent features similar to those of human breast cancer (3). It is therefore biologically plausible that some polycyclic aromatic hydrocarbons are absorbed by active and passive smokers as nitrosamines are (40) and concentrated for prolonged periods of time in the mammary ducts as other carcinogens are (41–43).

Nevertheless, the observed associations for active smoking are surprisingly strong in contrast to those of most previous studies. We discuss here the plausibility of the findings, first in light of the existing literature and then with respect to the strengths and weaknesses of our study.

Active smoking

In ever active smokers, there was a dose-response relation between the average lifetime number of cigarettes per day and the risk of breast cancer. Adjusted odds ratios ranged from 2.2 to 4.6. These are higher estimates than those reported in previous studies, most relative risk estimates ranging between 0.9 and 1.2 (4–24). For example, in the CASH Study (17), the odds ratio was 1.2 (95 percent CI 1.1–1.3) for ever active versus never active smoking.

However, with one exception (23), these studies did not measure the lifetime exposure to active smoke. Studies showing no, or nonstatistically significant, associations extrapolated lifetime smoking intake from summary questions about years when the woman started and eventually stopped smoking, as well as the average (or current) number of cigarettes smoked daily (5–8, 12, 16–21, 24). In the only other case-control study in which the lifetime history of smoking was

elicited for specific ages (23), the odds ratios of breast cancer for current active versus never active smokers were 1.2 (95 percent CI 0.7–1.9) for 1–15 cigarettes per day and 1.6 (95 percent CI 1.0–2.6) for ≥16 cigarettes per day. The corresponding odds ratios in the present study comparing current active with never active smokers (including passive smokers) were 1.0 and 1.9 (95 percent CI 1.2–3.1). Thus, a detailed assessment of lifetime exposure may be necessary to show the relation of active smoking with breast cancer.

The present results are not directly comparable with previous literature reports on active smoking and breast cancer since, to our knowledge, none of them separated passive smokers from subjects unexposed to active and passive smoke. Removing passive smokers from the referent category increased the odds ratio by a factor of 1.5–2.5 according to the active smoking category. It is therefore possible that the strength of the breast cancer-smoking association has been underestimated in the available body of literature. More studies using a similar approach to data collection and analysis are needed to determine what is the true strength of the association.

An inverse relation between the risk of breast cancer and the age at which active smoking began among heavy smokers (≥25 cigarettes per day) has been simultaneously observed in one study (20) but not in two others (21, 44). This finding was appealing because of its biologic plausibility; that is, the effect of carcinogens ought to be greater during adolescence, before the first birth, when an intense mammary gland differentiation takes place. In the present study, only 38 cases had smoked an average of ≥20 cigarettes per day. It was therefore not possible to examine the relation of the age at which smoking began among heavy smokers in our data. However, we found that the odds ratios related to either active smoking or passive smoking were similar whether the woman had started to smoke before or after the first birth.

Ex-active smokers had smoked less intensively than had current active smokers. Their odds ratios were increased compared with those unexposed to active and passive smoking, but there were no dose-responses related to the intensity of smoking or the time since they last smoked. This is intriguing, but it could be compatible with a slow clearance of carcinogens by the mammary gland, as suggested by analyses of breast fluid (41–43).

Passive smoking

The odds ratio of breast cancer in ever passive smokers was 3.2 (95 percent CI 1.7–5.9). As Smith et al. (24) found, we found no dose-response relations across levels of exposure to passive smoking.

Lifetime exposure to passive smoking is clearly difficult to assess. In the present study, to be classified as a passive smoker, a woman had to have been exposed at least 1 hour per day for 1 consecutive year or more. This definition was relatively strict in order to identify women with at least one period of substantial exposure in their lifetime. It was more difficult to assess accurately the number of hours per day of passive smoking, especially during leisure time. Misclassification of the intensity of exposure may therefore have diluted a possible dose-related effect.

For comparison purposes with the literature (25, 26), we computed the odds ratio of passive smoking among women ever married to an active smoker compared with women never married to an active smoker. The two-step odds ratio was 2.0 (95 percent CI 1.1–3.7) (not shown in a table). The lower bound of the confidence interval was consistent with the odds ratio of 1.4 computed by Wells (27). However, this proxy measure for passive smoking probably underestimates the association, since women married to nonactive smokers may have been exposed at home by someone other than their spouse. They also may have been exposed somewhere other than at home.

Being exposed to passive smoking 2 hours per day for 25 years was equivalent to having actively smoked an average of 20 cigarettes per day for 20 years. This was disturbing, since the effect of passive smoking was not a priori expected to be as strong as that of active smoking. A similar problem is encountered when studying cardiovascular diseases. Glantz and Parmley (45) found that the odds ratios of heart disease associated with passive smoking were high compared with those associated with active smoking. A better understanding of the biologic effect of tobacco smoke on the mammary gland is needed to decide whether this phenomenon reflects a different etiologic mechanism from that for lung cancer. Direct exposure to tar deposition should not be an issue for breast cancer or atherosclerosis.

We did not consider evaluating the effect of passive exposure in active smokers who were automatically exposed to the sidestream of their own cigarettes.

Confounding and potential biases

The risk factors of breast cancer (46) were incorporated as potential confounders in logistic regression models. Alcohol and saturated fat intakes were not strong confounders. The diet of cases was similar to that of controls, both being consistent with the results of a 1991 telephone survey conducted in the same target population (29). Case-control studies are not

optimal for assessing associations between diet and disease, but it is unlikely that residual confounding could explain all of the present results given the inconsistency of the literature on fat and breast cancer (47) and the weak association usually observed between alcohol and breast cancer (48).

The present study had limited statistical power to perform subgroup analyses. The effects of passive and active smoking were similar according to menopausal status. Among premenopausal women, multivariate odds ratios were 3.6 (95 percent CI 1.6–8.2) for ever passive and 3.5 (95 percent CI 1.5–7.8) for ever active smoking relative to women unexposed to active and passive smoke (not shown in a table). These odds ratios were similar to these in the full sample. Subgroup analyses were also conducted for all the variables in table 1. None of them indicated that the effects of passive and active smoking could be limited to a subgroup of women. However, the numbers were too small to fully adjust these analyses and did not allow computation of precise odds ratios for subgroups.

A strength of the present study design was to incorporate variables allowing us to quantify potential selection, detection, and recall biases. In order to assess a potential selection bias due to differential participation of cases and controls according to smoking status, we obtained the smoking status of women who refused to participate. The smoking status of nonparticipants was self-reported by controls and reported by physicians for cases. Among participants, 48 percent of cases and 40 percent of controls were ever active smokers. Among refusals, 49 percent of cases and 33 percent of controls were ever active smokers. The multivariate odds ratio of ever versus never active smoking was 1.6 (95 percent CI 1.2–2.2) in the study sample (n = 1,276) and 1.8 (95 percent CI 1.3–3.3) after adjustment for nonparticipation rates of ever and never smokers using a two-step procedure. This slightly conservative selection bias may be due to a small number of current smokers among nonparticipating controls being reluctant to tell their true smoking status.

The study design provided an additional means to assess a possible selection bias. Cases were expected to be representative of all cases newly diagnosed in the population, and controls were expected to be representative of the general population during that same period. It was therefore reassuring that the age distribution of interviewed cases was similar to that of eligible cases. Controls were similar to the general population for age, diet (29), parity (49), and active smoking (50). The proportions of never, current, and exsmokers were 61 percent, 23 percent, and 16 percent among controls and, respectively, 54 percent, 27 percent, and 19 percent (p = 0.15) in an independent telephone interview survey performed in September 1993 in a random sample of 315 living women aged 30–79 years (50).

A possible interviewer bias had been prevented to the extent that cases and controls were interviewed under the same conditions by interviewers who did not participate in recruitment and who were blind to the case-control status of the interviewees.

We also attempted to identify whether an overestimation of the odds ratio could have resulted from earlier detection of the disease among passive or active smokers because of more intense medical surveillance. There was no evidence of a potential detection bias among participants, since the proportions of node-positive tumors (p = 0.80) or of tumors with a diameter ≥2 cm (p = 0.41) were similar across smoking categories (table 4).

Available information did not support the existence of a differential recall of exposure between cases and controls strong enough to generate the observed association (51). It was postulated that if, for a similar exposure, cases were more likely to report having been passively exposed, they would also have stated that they were more preoccupied by passive smoke in their everyday life than were controls. There was no evidence for such recall bias. In the interview, the following question was included among others related to health behaviors. "What is your reaction to other people's smoke? That is, are you indifferent about it, or does it worry you?" Answers were similar for cases and controls (table 5). Among passive smokers, 49 percent of the controls and 52 percent of the cases reported worrying about passive smoking; among current active smokers, these proportions were 13 percent and 23 percent, respectively, for controls and cases. Unexposed women were more worried than were active smokers, but these differences in proportions across smoking categories were similar in cases and controls (p for interaction = 0.23).

Additional reasons downplay the role of a possible recall bias. A link between smoking and breast cancer

TABLE 4. Prevalence of node-positive tumors and of tumors ≥2 cm among the 244 cases, by smoking status, Geneva, Switzerland, January 1992 to October 1993

Smoking status	Node-positive tumors (%)	Tumors ≥2 cm (%)
Unexposed to active and passive smoke	50	43
Passive smoker	40	43
Ex-active smoker	46	30
Active smoker	43	41
χ^2 p value	0.80	0.41

TABLE 5. Proportion of cases and controls who said that they were worried about other people's smoke, among the 244 cases and 1,032 controls, by smoking status, Geneva, Switzerland, January 1992 to October 1993

Smoking status	Subjects reporting that they worried about passive smoking (%)	
	Cases	Controls
Unexposed to active and passive smoke	64	52
Passive smoker	52	49
Ex-active smoker	39	38
Active smoker	23	13
*p**	0.23	

* Logistic regression likelihood ratio test on the interaction between smoking and case-control status (N. E. Breslow and N. E. Day, eds. Statistical methods in cancer research. Vol. 1. Lyon: IARC, 1980. (IARC scientific publication no. 32)).

was unsuspected by most physicians. There had been no public advertising that smoking could be a hazard for the breast. There was little reason for cases to have systematically ruminated before this interview about whether their disease was related to active smoking and even less so to passive smoking.

Finally, separating passive smokers from unexposed women resulted in a group of 28 cases in the referent category. The odds of being unexposed (28/241 women = 0.12) drive the findings related to passive smoking. We were not able to identify a methodological flaw that could have generated the relatively small proportion of cases unexposed to active and passive smoke. The most serious consequence of an unsuspected bias for the present results would have been that some truly unexposed women had been classified as passive smokers. The structure of the questionnaire offered some protection against such bias. Subjects were asked to describe their passive exposure *only* if they had ever been continuously exposed at least 1 hour per day for at least 1 year. If we assume that, because of erroneous recall, 15 percent of the unexposed cases and 0 percent of the unexposed controls had been misclassified as passive smokers, the unbiased crude odds ratio for ever passive smoking would still be statistically significant (OR = 1.8, 95 percent CI 1.2–2.8). Thus, even extreme assumptions of misclassification do not jeopardize the overall direction of the study findings.

Biologic plausibility

The present study findings do not allow us to conclude that there is a causal association between smoking and breast cancer. There is no dose-response relation between the intensity of passive smoking and the odds ratio of breast cancer. The strengths of the associations for passive and active smoking are of similar magnitude, while one would expect the risk of one's own smoke to be much larger.

However, recent reports offer evidence that can reconcile these apparent incongruities with a plausible biologic mechanism. Ambrosone et al. (1) recently reported that active smoking increased the risk of breast cancer in women with a slow *N*-acetylation phenotype but not in rapid acetylators. About half of their population consisted of slow acetylators (1). Their susceptibility to carcinogenic components of the tobacco smoke may be increased, even for low doses (52). A similar prevalence of slow acetylation has been observed in Europe (52). We can speculate that women who develop breast cancer as a consequence of passive smoking are likely to be slow acetylators, rapid acetylators being able to metabolize low doses of the toxin. This hypothesis could be tested in a study in which information would be simultaneously available on the lifetime history of active and passive exposure to tobacco smoke as well as on the *N*-acetylation status.

The absence of a dose-response relation for passive smoking, if true, may be due to a low threshold of exposure among slow acetylators. Above that threshold, the risk associated with passive smoking would increase rapidly and then plateau. The latter hypothesis would also explain the relatively small magnitude of difference between the odds ratios for passive and active smoking.

Previous studies may have failed to demonstrate this association, because they did not collect information permitting either the removal of their referent group from passive smokers or stratification by the *N*-acetylation phenotype.

Public health significance

The decline in smoking prevalence over the last 10 years has been slower in women than in men (53). In Geneva, the proportion of men who smoke dropped from 51 percent in 1975 to 40 percent in 1985, but the decline is much weaker among women (31 percent in 1975 vs. 28 percent in 1985) (54). In our study, women with a higher formal education smoked more than did women of lower socioeconomic groups. This may indicate a still early phase of the epidemics when smoking is more common among the affluent population in contrast to later stages where it becomes associated with poverty (55), as in the United States (56). Thus, the tobacco smoking-breast cancer association is of major public health and clinical importance, since its elucidation will benefit the prevention of not only

breast cancer but also the rising epidemics of smoking-related diseases in women.

In conclusion, the present findings may be surprising, but they suggest that it is important to consider the effect of passive smoking when examining the association between active smoking and breast cancer. Previous studies may have failed to find an effect of active smoking, because they did not exclude passive smokers from the unexposed category. The association is not entirely explainable by analogy with the biologic mechanisms involved in established tobacco-related diseases. Additional studies of comparable design are needed to decide whether these intriguing findings are causal or not.

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REFERENCES

1. Ambrosone CB, Freudenheim JL, Marshall JR, et al. *N*-Acetyltransferase, cigarette smoking, and breast cancer risk. (Abstract). Proc Am Assoc Cancer Res 1995;36:283.
2. Calaf G, Russo J. Transformation of human breast epithelial cells by chemical carcinogens. Carcinogenesis 1993;14: 483–92.
3. Russo J, Tay LK, Russo IH. Differentiation of the mammary gland and susceptibility to carcinogenesis. Breast Cancer Res Treat 1982;2:5–73.
4. Vessey M, Baron J, Doll R, et al. Oral contraceptives and breast cancer: final report of an epidemiological study. Br J Cancer 1983;47:455–62.
5. Rosenberg L, Schwingi PJ, Kaufman DW, et al. Breast cancer and cigarette smoking. N Engl J Med 1984;310:92–4.
6. Smith EM, Sowers MF, Burns TL. Effects of smoking on the development of female reproductive cancers. J Natl Cancer Inst 1984;73:371–6.
7. Schechter MT, Miller AB, Howe GR. Cigarette smoking and breast cancer: a case-control study of screening program participants. Am J Epidemiol 1985;121:479–87.
8. Brinton LA, Schairer C, Stanford JL, et al. Cigarette smoking and breast cancer. Am J Epidemiol 1986;123:614–22.
9. Hiatt RA, Fireman BH. Smoking, menopause, and breast cancer. J Natl Cancer Inst 1986;76:833–8.
10. O'Connell DL, Hulka BS, Chambless LE, et al. Cigarette smoking, alcohol consumption, and breast cancer risk. J Natl Cancer Inst 1987;78:229–34.
11. Stockwell HG, Lyman GH. Cigarette smoking and the risk of female reproductive cancer. Am J Obstet Gynecol 1987;157: 35–40.
12. Adami HO, Lund E, Bergstrom R, et al. Cigarette smoking, alcohol consumption, and risk of breast cancer in young women. Br J Cancer 1988;58:832–7.
13. Brownson RC, Blackwell CW, Pearson DK, et al. Risk of breast cancer in relation to cigarette smoking. Arch Intern Med 1988;148:140–4.
14. London SJ, Colditz GA, Stampfer MJ, et al. Prospective study of smoking and the risk of breast cancer. J Natl Cancer Inst 1989;81:1625–31.
15. Meara J, McPherson K, Roberts M, et al. Alcohol, cigarette smoking, and breast cancer. Br J Cancer 1989;60:70–3.
16. Schechter MT, Miller AB, Howe GR, et al. Cigarette smoking and breast cancer: case-control studies of prevalent incident cancer in the Canadian National Breast Screening Study. Am J Epidemiol 1989;130:213–20.
17. Chu SY, Stroup NE, Wingo PA, et al. Cigarette smoking and the risk of breast cancer. Am J Epidemiol 1990;131:244–53.
18. Ewertz M. Smoking and breast cancer risk in Denmark. Cancer Causes Control 1990;1:31–7.
19. Vatten LJ, Kvinnsland S. Cigarette smoking and risk of breast cancer: a prospective study of 24,329 Norwegian women. Eur J Cancer 1990;26:830–3.
20. Palmer JR, Rosenberg L, Clarke EA, et al. Breast cancer and cigarette smoking: a hypothesis. Am J Epidemiol 1991;134: 1–13.
21. Field NA, Baptiste MS, Nasca PC, et al. Cigarette smoking and breast cancer. Int J Epidemiol 1992;21:842–8.
22. Calle EE, Miracle-McMahill HL, Thun MJ, et al. Cigarette smoking and risk of fatal breast cancer. Am J Epidemiol 1994;139:1001–7.
23. Rohan TE, Baron JA. Cigarette smoking and breast cancer. Am J Epidemiol 1989;129:36–42.
24. Smith SJ, Deacon JM, Chilvers CED, et al. Alcohol, smoking, passive smoking, and caffeine in relation to breast cancer risk in young women. Br J Cancer 1994;70:112–19.
25. Sandler DP, Everson RB, Wilcox AJ. Cigarette smoking and breast cancer. (Letter). Am J Epidemiol 1986;123:370–1.
26. Hirayama T. Cancer de mama: avances en diagnostico y tratamiento. In: Diaz-Faes J, ed. Epidemiologia y factores de riesgo del cancer de mama. (In Spanish). Léon, Spain: Santiago Garcia, 1990:21–38.
27. Wells AJ. Breast cancer, cigarette smoking, and passive smoking. (Letter). Am J Epidemiol 1991;133:208–10.
28. Block G, Hartman AM, Dresser CM, et al. A data-based approach to diet questionnaire design and testing. Am J Epidemiol 1986;124:453–69.
29. Bernstein M, Morabia A, Costanza MC, et al. The nutritional balance of the diet of the adult population of Geneva. Soz Praventivmed 1994;39:333–44.
30. Morabia A, Bernstein M, Kumanyika S, et al. Development and validation of a semi-quantitative food frequency questionnaire on the basis of a population survey. Soz Praventivmed 1994;39:345–69.
31. Breslow NE, Day NE, eds. Statistical methods in cancer research. Vol 1. The analysis of case-control studies. Lyon: International Agency for Research on Cancer, 1980. (IARC scientific publication no. 32).
32. Breslow NE, Cain KC. Logistic regression for two-stage case-

control data. Biometrika 1988;75:11–20.
33. Cain KC, Breslow NE. Logistic regression analysis and efficient design for two-stage studies. Am J Epidemiol 1988;128: 1198–206.
34. Armitage P, Berry G. Statistical methods in medical research. 2nd ed. Oxford: Blackwell, 1987.
35. SAS Institute, Inc. SAS user's guide: basics and statistics, version 6 ed. Cary, NC: SAS Institute, Inc, 1989.
36. Tobacco. In: Tomatis L, ed. Cancer: causes, occurrence, and control. Lyon: International Agency for Research on Cancer, 1990:169–180. (IARC scientific publication no. 100).
37. Vu-Duc T, Huynh CK. Sidestream tobacco smoke constituents in indoor air modelled in an experimental chamber—polycyclic aromatic hydrocarbons. Environ Int 1989;15:57–64.
38. Polynuclear aromatic compound. Part 1. Chemical, environmental, and experimental data. IARC Monogr Eval Carcinog Risk Chem Hum 1983;32:211–24.
39. Huggins CB. Selective induction of hormone-dependent mammary adenocarcinoma in the rat. J Lab Clin Med 1987;109: 262–6.
40. Hecht SS, Carmella SG, Murphy SE, et al. A tobacco-specific lung carcinogen in the urine of men exposed to cigarette smoke. N Engl J Med 1993;329:1543–6.
41. Petrakis NL, Gruenke LD, Beelen TC, et al. Nicotine in breast fluid of nonlactating women. Science 1978;199:303–4.
42. Petrakis NL, Maack CA, Lee RE, et al. Mutagenic activity in nipple aspirates of human breast fluid. Cancer Res 1980;40: 188–9.
43. Petrakis NL. Nipple aspirate fluid in epidemiologic studies of breast disease. Epidemiol Rev 1993;15:188–95.
44. Ewertz M. Re: "Breast cancer and cigarette smoking: a hypothesis." (Letter). Am J Epidemiol 1992;135:1185.
45. Glantz SA, Parmley WW. Passive smoking and heart disease. Mechanisms and risk. JAMA 1995;273:1047–53.
46. Kelsey JL. Breast cancer epidemiology: summary and future directions. Epidemiol Rev 1993;15:256–63.
47. Hunter DJ, Willett WC. Diet, body size, and breast cancer. Epidemiol Rev 1993;15:110–32.
48. Rosenberg L, Metzger LS, Palmer JR. Alcohol consumption and risk of breast cancer: a review of the epidemiologic evidence. Epidemiol Rev 1993;15:133–44.
49. Neury JE. "Nouvelles" familles genevoises. (In French). Geneva: Service Cantonal de Statistique, 1991:9. (Document no. 13).
50. Institut für Praxisorientierte Sozial-und-Marktforschung (IPSO). Consumption of tobacco and alcohol in the Geneva population. (In French). Geneva: IPSO, 1993.
51. Drews CD, Greenland S. The impact of differential recall on the results of case-control studies. Int J Epidemiol 1990;19: 1107–12.
52. Vineis P, Bartsch H, Caporaso N, et al. Genetically based *N*-acetyltransferase metabolic polymorphism and low-level environmental exposure to carcinogens. Nature 1994;369: 154–6.
53. Pierce JP. International comparisons of trends in cigarette smoking prevalence. Am J Public Health 1989;79:152–7.
54. Morabia A, Landis JR, Bernstein M, et al. Has prevention of smoking among women been neglected? (In French). Tuber Lung Dis 1992;6:54–7.
55. Barker DJP. Rise and fall of Western diseases. Nature 1989; 338:371–2.
56. Samet JM. Editorial commentary: new effects of active and passive smoking on reproduction? Am J Epidemiol 1991;133: 348–50.