Active Smoking, Household Passive Smoking, and Breast Cancer: Evidence From the California Teachers Study

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Background: **There is great interest in whether exposure to tobacco smoke, a substance containing human carcinogens, may contribute to a woman's risk of developing breast cancer. To date, literature addressing this question has been mixed, and the question has seldom been examined in large prospective study designs.** ***Methods:*** **In a 1995 baseline survey, 116 544 members of the California Teachers Study (CTS) cohort, with no previous breast cancer diagnosis and living in the state at initial contact, reported their smoking status. From entry into the cohort through 2000, 2005 study participants were newly diagnosed with invasive breast cancer. We estimated hazard ratios (HRs) for breast cancer associated with several active smoking and household passive smoking variables using Cox proportional hazards models.** ***Results:*** **Irrespective of whether we included passive smokers in the reference category, the incidence of breast cancer among current smokers was higher than that among never smokers (HR = 1.32, 95% confidence interval [CI] = 1.10 to 1.57 relative to all never smokers; HR = 1.25, 95% CI = 1.02 to 1.53 relative to only those never smokers who were unexposed to household passive smoking). Among active smokers, breast cancer risks were statistically significantly increased, compared with all never smokers, among women who started smoking at a younger age, who began smoking at least 5 years before their first full-term pregnancy, or who had longer duration or greater intensity of smoking. Current smoking was associated with increased breast cancer risk relative to all nonsmokers in women without a family history of breast cancer but not among women with such a family history. Breast cancer risks among never smokers reporting household passive smoking exposure were not greater than those among never smokers reporting no such exposure.** ***Conclusion:*** **Our study provides evidence that active smoking may play a role in breast cancer etiology and suggests that further research into the connection is warranted, especially with respect to genetic susceptibilities. [J Natl Cancer Inst 2004;96:29–37]**

Breast cancer is the most frequently diagnosed cancer in women *(1,2)* and its incidence has increased over the past two decades *(3)*. Changes in breast cancer rates over time and among migrants, as well as the finding that geographical areas differ in incidence, suggest that environmental factors may play a role in breast cancer etiology *(4–8)*. Tobacco is one of the most widely examined environmental exposures for disease risk. Despite considerable research, however, the relationship of tobacco exposures to breast cancer incidence remains controversial *(9–16)*.

Tobacco smoke contains a number of human carcinogens *(17)*, and metabolites of cigarette smoke have been found in the breast fluid of smokers *(18,19)*. However, smoking also has anti-estrogenic effects *(20–25)* that could, paradoxically, act to lower breast cancer risk. Recently, a number of studies have reported that smoking increases breast cancer risk only in women who began smoking at an early age *(26–32)* or before (or during) a first pregnancy *(33–35)*, when breast epithelial tissue is thought to be especially susceptible to damage from environmental insults *(29,36–38)*. Other studies have reported that smoking increases the risk of breast cancer only in young women *(27,28)* or women with a family history of breast cancer *(39)*. The inconsistencies in the literature may be due to heterogeneity of risk according to timing of exposure, age of diagnosis, or genetic susceptibilities. Furthermore, many of the earlier active smoking studies failed to take into account passive smoking exposures among nonsmokers, that is, exposure to the cigarette smoke of others *(40,41)*. If, as some studies *(11,35,42,43)* have suggested, passive smoking is also related to breast cancer risk, we would expect that failing to exclude passive smokers from the analysis would dilute risk estimates for active smoking *(9–11)*.

We examined the breast cancer risk associated with active and passive smoking in the California Teachers Study (CTS) cohort, a large cohort of female professional school employees. This cohort was designed specifically to study breast cancer etiology. The extensive information collected by the CTS on tobacco use, coupled with the highly detailed information collected on other important breast cancer risk factors, offered us the opportunity to address a number of the hypotheses still unanswered following these recent reports *(9–16)*. Specifically, we examined the independent relationship between both active and passive smoking and breast cancer incidence in this cohort of women. Our analyses included evaluations of the timing of exposure and considered, separately, breast cancer in pre- and

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postmenopausal women and in women with and without a family history of breast cancer. In our analyses of active smoking variables, we also examined the effect of alternately including and excluding passive smokers in the referent category.

METHODS

Study Population

The CTS cohort was established from respondents to a 1995 mailing to all 329 000 active and retired female enrollees in the California State Teachers Retirement System (CalSTRS). CalSTRS Defined Benefit Program members include California public school employees who teach at the kindergarten through community college levels, are involved in the selection and preparation of instructional materials for these levels, or supervise persons engaged in these activities. Enrollment in the CTS with completed baseline questionnaires was 133 479 (41%). A full description of the CTS cohort is available elsewhere *(44)*. Use of human subjects data in this study was reviewed by the California Health and Human Services Agency, Committee for the Protection of Human Subjects, and was found to be in compliance with their ethical standards as well as with the U.S. Code of Federal Regulations, Title 45, Part 46, on the Protection of Human Subjects.

Outcome Assessment

The CTS cohort is followed annually for cancer diagnosis, death, and change of address. Cancer outcomes are identified through annual linkage with the California Cancer Registry (CCR), a legislatively mandated statewide population-based cancer reporting system *(45)*. Modeled after the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program, the CCR maintains high standards for data quality and completeness and is estimated to be 99% complete *(46)*. Linkage between the CTS cohort and the CCR database is based on full name, date of birth, address, and Social Security number; it includes a manual review of possible matches. Mortality files, as well as reports from relatives, are used to ascertain date and cause of death. Changes of address are obtained by annual mailings, responses from participants, and linkages to the U.S. Postal Service National Change of Address database. For our analysis, we defined a case subject as any woman diagnosed with invasive breast cancer after the date she completed her baseline questionnaire through December 31, 2000. We excluded women who were diagnosed with invasive or *in situ* breast cancer before joining the cohort (N = 6171).

Calculation of Follow-up

We based person-months at risk on the first 5 years of follow-up. Person-months were calculated as the number of months between the time a woman joined the cohort (i.e., the date she completed her baseline survey) and the earliest of four dates: the date of her breast cancer diagnosis, the date of her first non-California address, the date of her death, or December 31, 2000. Women diagnosed with *in situ* breast cancer during the follow-up period were censored at the time of their diagnoses.

Active smoking status. We classified women's active smoking status based on their answers to two questions from their baseline surveys. Respondents were asked if they had ever smoked 100 or more cigarettes during their lifetime and, if so, when they started and stopped smoking. Based on their responses, respondents were categorized as never, former, or current smokers.

Active smoking history. The baseline survey also collected information on active smoking history among the former and current smokers. We categorized the average number of cigarettes smoked per day (i.e., smoking intensity) during the period that the women smoked as less than 10, 10–19, and 20 or more. We categorized both total years of smoking and smoking pack-years (i.e., number of packs smoked per day times number of years smoked) as 10 or less, 11–20, 21–30, and 31 or more. We categorized age at smoking initiation as less than 20 years and 20 or more years. Former smokers reported the number of years since they quit; we categorized this variable as less than 5 years, 5–9 years, 10–19 years, and 20 or more years. Additionally, for parous cohort members, we constructed variables characterizing active smoking behavior in relation to the time of their first full-term pregnancy. Parous women were categorized into the following hierarchical groups: parous never smoker (referent); pre-partum smoker for less than 5 years; pre-partum smoker for 5 or more years; and postpartum-only smoker. Because we constructed this variable from the responses to two different questions (age at first live birth and age at smoking initiation), our data were not sufficiently precise to create a variable representing women who smoked only during their first pregnancy. However, the number of women in this category is likely to be small.

Passive smoking exposure. We categorized never smokers into two groups: those with exposure to household passive smoking and those without such exposure. Household passive smoking exposure was based on the women's report of ever having lived with a smoker. Women also reported on the period of household passive smoking exposure, and we further grouped them into categories of no exposure, only childhood exposure, only adulthood exposure, and both childhood and adulthood exposure.

Personal risk factors. Age was broken into four categories: less than 45 years old; 45–54 years old; 55–64 years old; and 65 years old or older. Race/ethnicity was divided into five categories: non-Hispanic white; African American; Hispanic; Asian/Pacific Islander; and other/not provided. Family history of breast cancer was defined as breast cancer in a first-degree relative; this variable was summarized as yes, no, and adopted/not provided. Women's age at menarche was categorized as less than 12 years old, 12–13 years old, 14 years old or older, and not provided. Pregnancy history was described as either nulliparous or parous, with six categories for age at first full-term pregnancy: less than 20 years old; 20–24 years old; 25–29 years old; 30–34 years old; 35 years old or older; and unknown age. Physical activity, defined as the average number of hours per week of moderate or strenuous activity over a woman's lifetime, was categorized as none, less than 2 hours per week, 2–4 hours per week, 5 or more hours per week, and not provided. Women were grouped into tertiles according to body mass index (BMI): less than 25.8 kg/m^2, 25.8–32.2 kg/m^2, 32.3 kg/m^2 or more, and height or weight not provided. Women's menopausal status was defined as pre-/perimenopausal, postmenopausal, and not able to determine. To account for the different risks associated with BMI for pre-/peri- and postmenopausal women, we included six terms representing the joint levels for BMI and menopausal status in

the model, with our reference group consisting of pre-/perimenopausal women with a BMI of less than 25.8 kg/m^2. Alcohol consumption categories, measured in grams per day, included nondrinkers, consumers of less than 5 grams per day, 5–9 grams per day, 10–14 grams per day, 15–19 grams per day, 20 grams or more per day, and unknown/missing. We categorized women's hormone therapy use as never used estrogens (with separate categories for women <50 years old and ≥50 years old), used estrogens for 5 years or less, used estrogens for more than 5 years, and unable to determine.

Statistical Analysis

We limited our statistical analyses to those CTS members who were living in California at the time that they completed their baseline questionnaire, who had no personal history of breast cancer, and who provided sufficient information on the baseline survey to determine active smoking status (N = 116 544). The analysis of passive smoking was limited to lifetime never smokers who provided complete household passive smoking exposure information. Using the frequency procedure in SAS *(47)*, we evaluated the distribution of the active and passive smoking exposure categories, active smoking history, period of passive smoking exposure, and personal risk factors among cohort members. We estimated hazard ratios (HRs) and 95% confidence intervals (CIs) associated with active and passive smoking exposure using Cox proportional hazards regression models. Examination of Kaplan–Meier survival curves and log-minus-log survival plots indicated no apparent violation of the underlying assumption of proportional hazards on which the Cox regression model is predicated *(48,49)*. We calculated hazard ratios for active smoking status both with and without inclusion of passive smokers in our referent category of never smokers. Where appropriate, we performed linear tests for trend across categories of exposure, modeling levels of exposure as an ordinal variable. We adjusted our multivariable models for the personal risk factors of interest (age, race, family history of breast cancer, age at menarche, pregnancy history, physical activity, BMI, menopausal status, BMI and menopausal status interaction, alcohol consumption, and hormone therapy use). We repeated these same analyses separately for pre-/peri- and postmenopausal women. Additional Cox modeling was performed, stratifying on family history of breast cancer. Formal tests of two-way statistical interactions were performed by conducting likelihood ratio tests comparing the model fit with and without an interaction term. We used SAS version 8.1 to perform all our analyses *(47)*. All statistical tests were two-sided, and *P* values less than .05 were considered statistically significant.

Results

We identified 2005 breast cancer case subjects among the 116 544 eligible CTS cohort members included in our active smoking analysis. Among the subset of never-smoking women who provided detailed information on timing of household passive smoking (N = 76 189), we identified 1150 breast cancer case subjects to include in our detailed passive smoking analyses. The cohort is predominantly non-Hispanic white (87%), and approximately half is postmenopausal. We noted no substantial differences in demographic characteristics or risk profiles between the subset of the cohort analyzed here and that reported in the baseline analyses *(44)* (data not shown).

Table 1 shows the distribution of smoking status among the cohort members. Overall, 67% of study subjects were lifetime nonsmokers, 28% were former smokers, and 5% were active smokers at the time they completed their baseline questionnaire (referred to henceforth as "current smokers"). The prevalence of never smokers was lower among women who developed breast cancer (59%) than among those who did not (67%), although the prevalence of current smokers was approximately the same in both groups (7% and 5%, respectively). Among lifetime nonsmokers, approximately 70% reported some household passive smoking exposure.

Table 2 presents the adjusted hazard ratios for breast cancer associated with household passive smoking exposure among lifetime never smokers. Hazard ratios were close to unity for all passive smoking exposure categories examined (HRs ranged from 0.87 to 1.01 and were not statistically significant). Risk estimates did not appear to vary for different periods of exposure (i.e., childhood versus adulthood) or by menopausal status. There was no evidence of interaction between menopausal status and passive smoking exposures (all $P>.10$; data not shown).

We first evaluated the risk of breast cancer associated with active smoking status both including and excluding passive smokers in our never smoker referent category (Table 3). Regardless of the referent category used, current smokers exhibited a statistically significantly increased risk of breast cancer (HR = 1.32, 95% CI = 1.10 to 1.57, relative to all never smokers; HR = 1.25, 95% CI = 1.02 to 1.53, relative to never smokers who were not exposed to household passive smoking). Stratification by menopausal status suggested that the association of

Table 1. Distribution of active and passive smoking status among California Teachers Study (CTS) cohort members (N = 116 544)*

	Entire cohort	Breast cancer cases†	Cohort members without breast cancer
Smoking status	N (%)	N (%)	N (%)
Never smokers	77 708 (67)	1174 (59)	76 534 (67)
No passive exposure	22 659 (29)‡	316 (27)‡	22 343 (29)‡
Some passive exposure	54 421 (70)‡	848 (72)‡	53 573 (70)‡
Unknown passive exposure	628 (1)‡	10 (1)‡	618 (1)‡
Former smokers	32 929 (28)	690 (34)	32 239 (28)
Current smokers	5907 (5)	141 (7)	5766 (5)
Total	116 544 (100)	2005 (100)	114 539 (100)

*Limited to CTS cohort members living in California at baseline without a previous history of breast cancer who provided valid data on active and passive smoking status.

†Cases diagnosed prospectively, 1996–2000.

‡Percentage of never smokers.

Table 2. Hazard ratios (HRs) and 95% confidence intervals (CIs) for invasive breast cancer incidence and exposure to household passive smoking among California Teachers Study (CTS) cohort members*

Period of household passive smoking exposure among never smokers	Full study sample†		Pre-/perimenopausal at baseline		Postmenopausal at baseline	
	No. of cases	HR‡ (95% CI)	No. of cases	HR§ (95% CI)	No. of cases	HR§ (95% CI)
Never exposed	316	1.00 (referent)	78	1.00 (referent)	205	1.00 (referent)
Only childhood exposure	307	0.92 (0.78 to 1.07)	96	0.93 (0.69 to 1.26)	180	0.93 (0.76 to 1.14)
Only adulthood exposure	211	0.94 (0.79 to 1.12)	31	1.01 (0.66 to 1.54)	161	0.88 (0.71 to 1.08)
Childhood and adulthood exposure	316	0.93 (0.79 to 1.09)	49	0.87 (0.60 to 1.25)	232	0.91 (0.76 to 1.12)

*Limited to never-smoking CTS cohort members living in California at baseline without a previous history of breast cancer who provided valid smoking data and detailed data on timing of household passive smoking exposures (N = 76 189).

†Full sample includes women with indeterminable menopausal status at baseline (coded as unknown).

‡Multivariable model was adjusted for age, race, family history of breast cancer, age at menarche, parity, age at first full-term pregnancy, physical activity, alcohol consumption, body mass index (BMI), menopausal status, BMI and menopausal status interaction, and hormone therapy use.

§Multivariable model was adjusted for age, race, family history of breast cancer, age at menarche, parity, age at first full-term pregnancy, physical activity, alcohol consumption, BMI, and hormone therapy use.

current smoking with increased breast cancer risk may be limited to postmenopausal women, although the likelihood ratio statistic indicated that there was no statistically significant interaction between smoking status and menopausal status ($P>.10$). The hazard ratios for breast cancer among former smokers were slightly elevated but were not statistically significant, either in the entire sample (HR = 1.08, 95% CI = 0.98 to 1.19, relative to all never smokers; HR = 1.03, 95% CI = 0.89 to 1.18, relative to never smokers who were not exposed to passive smoking) or when stratified by menopausal status. There was no evidence of an association with any household passive smoking (HR = 0.94, 95% CI = 0.82 to 1.07, for any household passive smoking compared with none). Risk estimates from initial models that adjusted for only age and race (data not shown) were similar to those from the fully adjusted models reported here. Additional adjustment for the entire set of covariates had the effect of moving the point estimates slightly closer to 1.0. Because we saw no evidence for a passive smoking effect on breast cancer risk and no evidence that including passive smokers in our referent group affected risk estimates for active smoking status, we performed all subsequent analyses of active smoking history using the entire group of never smokers as the referent group.

We analyzed active smoking history measures individually in multivariable models (Table 4). Smoking intensity (i.e., cigarettes per day) appeared to be related to breast cancer risk. A statistically significant hazard ratio was seen in the full study sample (HR = 1.22, 95% CI = 1.05 to 1.42) and in both menopausal groups for those women averaging 20 or more cigarettes smoked per day during the time that they smoked relative to all never smokers. The test for linear trend across categories of cigarettes smoked per day was statistically significant in the entire study sample ($P = .004$) and in the postmenopausal group ($P = .037$), and it almost reached statistical significance among the pre-/perimenopausal group ($P = .081$). There was no evidence of statistical interaction between smoking intensity and menopausal status ($P = .42$, data not shown).

Duration of smoking appeared to be related to breast cancer risk in the full sample ($P_{trend} = .009$) and among postmenopausal women ($P_{trend} = .032$) but not among pre-/perimenopausal women ($P_{trend} = .616$), although no statistical interaction with menopausal status was found ($P = .80$; data not shown).

Table 3. Hazard ratios (HRs) and 95% confidence intervals (CIs) for invasive breast cancer associated with active smoking status with and without exclusion of passive smokers from the never-smoking referent category*

Tobacco exposure	Full study sample†		Pre-/perimenopausal at baseline		Postmenopausal at baseline	
	No. of cases	HR‡ (95% CI)	No. of cases	HR§ (95% CI)	No. of cases	HR§ (95% CI)
Passive smokers included in reference category						
Never smokers	1174	1.00 (referent)	258	1.00 (referent)	796	1.00 (referent)
Former smokers	690	1.08 (0.98 to 1.19)	108	1.12 (0.89 to 1.42)	512	1.07 (0.95 to 1.20)
Current smokers	141	1.32 (1.10 to 1.57)	15	1.02 (0.60 to 1.72)	106	1.29 (1.05 to 1.58)
Passive smokers excluded from reference category						
Never smokers with no passive exposure	316	1.00 (referent)	78	1.00 (referent)	205	1.00 (referent)
Never smokers with passive exposure	848	0.94 (0.82 to 1.07)	179	0.93 (0.71 to 1.22)	583	0.92 (0.78 to 1.08)
Former smokers	690	1.03 (0.89 to 1.18)	108	1.07 (0.79 to 1.44)	512	1.01 (0.85 to 1.19)
Current smokers	141	1.25 (1.02 to 1.53)	15	0.96 (0.55 to 1.68)	106	1.21 (0.95 to 1.54)

*Limited to California Teachers Study (CTS) cohort members living in California at baseline without a previous history of breast cancer who provided valid data on active and passive smoking status. There are 2005 cases in the analyses with passive smokers included in the reference category and 1995 cases in the analyses with passive smokers excluded (the latter group was restricted to women for whom some information on passive exposure was available).

†Full sample includes women with indeterminable menopausal status at baseline (coded as unknown).

‡Multivariable model was adjusted for age, race, family history of breast cancer, age at menarche, parity, age at first full-term pregnancy, physical activity, alcohol consumption, body mass index (BMI), menopausal status, BMI and menopausal status interaction, and hormone therapy use.

§Multivariable model was adjusted for age, race, family history of breast cancer, age at menarche, parity, age at first full-term pregnancy, physical activity, alcohol consumption, BMI, and hormone therapy use.

Table 4. Hazard ratios (HRs) and 95% confidence intervals (CIs) for invasive breast cancer associated with active smoking history among California Teachers Study (CTS) members*

Active smoking history	Full study sample†		Pre-/perimenopausal at baseline		Postmenopausal at baseline	
	No. of cases	HR‡ (95% CI)	No. of cases	HR§ (95% CI)	No. of cases	HR§ (95% CI)
Never smokers	1174	1.00 (referent)	258	1.00 (referent)	796	1.00 (referent)
Smoking intensity (average No. of cigarettes per day)						
<10	343	1.04 (0.92 to 1.18)	52	0.97 (0.72 to 1.32)	257	1.06 (0.92 to 1.22)
10–19	260	1.14 (0.99 to 1.30)	35	1.08 (0.75 to 1.54)	193	1.11 (0.95 to 1.31)
≥20	209	1.22 (1.05 to 1.42)	34	1.50 (1.04 to 2.15)	153	1.18 (0.99 to 1.41)
		P_{trend} = .004		P_{trend} = .081		P_{trend} = .037
Total No. of smoking years						
≤10	176	0.99 (0.85 to 1.17)	52	1.14 (0.85 to 1.55)	101	0.95 (0.77 to 1.17)
11–20	193	1.17 (1.00 to 1.37)	33	1.10 (0.76 to 1.58)	140	1.22 (1.02 to 1.47)
21–30	163	1.17 (0.99 to 1.38)	21	1.06 (0.67 to 1.66)	113	1.07 (0.88 to 1.31)
≥31	251	1.15 (1.00 to 1.33)	7	0.99 (0.46 to 2.13)	230	1.16 (0.99 to 1.34)
		P_{trend} = .009		P_{trend} = .616		P_{trend} = .032
No. of smoking pack-years						
≤10	338	1.02 (0.91 to 1.16)	67	1.03 (0.78 to 1.35)	231	1.02 (0.88 to 1.18)
11–20	165	1.24 (1.05 to 1.46)	26	1.31 (0.87 to 1.98)	124	1.23 (1.02 to 1.50)
21–30	94	1.12 (0.91 to 1.39)	4	0.46 (0.17 to 1.24)	75	1.13 (0.89 to 1.44)
≥31	173	1.25 (1.06 to 1.47)	15	2.05 (1.20 to 3.49)	144	1.19 (0.99 to 1.42)
		P_{trend} = .002		P_{trend} = .136		P_{trend} = .019
Years since quitting smoking						
≥20	352	1.08 (0.95 to 1.22)	44	1.19 (0.86 to 1.66)	274	1.06 (0.92 to 1.22)
10–19	179	1.08 (0.92 to 1.27)	33	1.02 (0.71 to 1.47)	123	1.07 (0.88 to 1.29)
5–9	79	1.23 (0.97 to 1.54)	15	1.39 (0.82 to 2.35)	57	1.23 (0.93 to 1.61)
<5	39	0.80 (0.58 to 1.11)	7	0.78 (0.37 to 1.66)	29	0.87 (0.60 to 1.26)
		P_{trend} = .480		P_{trend} = .677		P_{trend} = .472
Age of smoking initiation						
≥20	285	1.03 (0.90 to 1.17)	31	1.00 (0.68 to 1.46)	232	1.03 (0.89 to 1.20)
<20	507	1.17 (1.05 to 1.30)	82	1.13 (0.88 to 1.46)	359	1.16 (1.02 to 1.32)
Smoking in relation to timing of first pregnancy‖						
Smoked pre-partum <5 y	110	0.99 (0.80 to 1.21)	10	1.04 (0.53 to 2.03)	93	1.01 (0.81 to 1.26)
Smoked pre-partum ≥5 y	406	1.13 (1.00 to 1.28)	60	1.01 (0.75 to 1.36)	298	1.15 (0.99 to 1.33)
Smoked postpartum only	42	0.89 (0.65 to 1.21)	3	0.94 (0.29 to 3.02)	37	0.90 (0.64 to 1.26)

*Limited to CTS cohort members living in California at baseline without a previous history of breast cancer who provided valid smoking data.

†Full sample includes women with indeterminable menopausal status at baseline (coded as unknown).

‡Multivariable model was adjusted for age, race, family history of breast cancer, age at menarche, parity, age at first full-term pregnancy, physical activity, alcohol consumption, body mass index (BMI), menopausal status, BMI and menopausal status interaction, and hormone therapy use.

§Multivariable model was adjusted for age, race, family history of breast cancer, age at menarche, parity, age at first full-term pregnancy, physical activity, alcohol consumption, BMI, and hormone therapy use.

‖Reference group comprised 883 parous never smokers.

Pack-years of smoking was associated with elevated hazard ratios overall (P_{trend} = .002) and among postmenopausal women (P_{trend} = .019). Among pre-/perimenopausal women, the hazard ratio for the highest category of pack-years (i.e., ≥31 pack-years) was statistically significantly elevated (HR = 2.05, 95% CI = 1.20 to 3.49), although the test for trend was not statistically significant (P = .136). The likelihood ratio test for interaction between pack-years and menopausal status was close to but did not reach statistical significance (P = .07; data not shown).

Among former smokers, the number of years since quitting smoking did not appear to be related to breast cancer risk in the full sample or in either menopausal group. The hazard ratio point estimates for the different time intervals since quitting ranged from 0.78 to 1.39, with all 95% confidence intervals including 1.0 and with statistically nonsignificant tests for trend. We also found no interaction between years since quitting and menopausal status (P = .76; data not shown).

Compared with never smokers, women who started smoking at age 20 or older did not show an increased risk of breast cancer (HR = 1.03, 95% CI = 0.90 to 1.17). Women who started smoking before age 20 had a statistically significant increase in their risk of breast cancer (HR = 1.17, 95% CI = 1.05 to 1.30). In stratified analyses, point estimates of risk associated with early smoking initiation were similar among pre-/perimenopausal and postmenopausal women.

We found some evidence that women who smoked before their first full-term pregnancy increased their risk of breast cancer, but this effect was restricted to those who smoked for at least 5 years before their first full-term pregnancy (HR = 1.13, 95% CI = 1.00 to 1.28). When we stratified the data by menopausal status, this effect was limited to postmenopausal women (postmenopausal women: HR = 1.15, 95% CI = 0.99 to 1.33; pre-/perimenopausal women: HR = 1.01, 95% CI = 0.75 to 1.36), although no evidence of statistical interaction between smoking before a first pregnancy and menopausal status was found (P = .84; data not shown). Hazard ratios for women who started smoking after their first full-term pregnancy did not differ from unity (HR = 0.89, 95% CI = 0.65 to 1.21).

Finally, we examined the relationship between active smoking status and the risk of breast cancer separately in women with (12%) and without (88%) a family history of breast cancer (Table 5). Among women without such a family history, current smoking was associated with a statistically significant increase

Table 5. Hazard ratios (HRs) and 95% confidence intervals (CIs) for invasive breast cancer incidence associated with active smoking status stratified by family history of breast cancer among California Teachers Study (CTS) members*

	Full study sample†		Pre-/perimenopausal at baseline		Postmenopausal at baseline	
Active smoking status	No. of cases	HR‡ (95% CI)	No. of cases	HR§ (95% CI)	No. of cases	HR§ (95% CI)
Without family history of breast cancer (N = 98 478)						
Never smoker	894	1.00 (referent)	200	1.00 (referent)	600	1.00 (referent)
Former smoker	543	1.11 (0.99 to 1.24)	81	1.10 (0.84 to 1.43)	409	1.12 (0.98 to 1.27)
Current smoker	110	1.35 (1.11 to 1.65)	11	0.94 (0.51 to 1.74)	85	1.39 (1.10 to 1.75)
With family history of breast cancer (N = 13 684)						
Never smoker	240	1.00 (referent)	49	1.00 (referent)	169	1.00 (referent)
Former smoker	115	0.87 (0.69 to 1.10)	22	1.06 (0.63 to 1.80)	80	0.81 (0.61 to 1.06)
Current smoker	26	1.19 (0.79 to 1.79)	4	1.47 (0.52 to 4.13)	17	0.95 (0.57 to 1.57)

*Limited to CTS cohort members living in California at baseline without a previous history of breast cancer who provided valid smoking data. Women who were adopted or did not provide information on family history of breast cancer were excluded from this analysis. Family history was defined as breast cancer in a first-degree relative. A total of 112 162 women were included in this analysis.

†Full sample includes women with indeterminable menopausal status at baseline.

‡Multivariable model was adjusted for age, race, age at menarche, parity, age at first full-term pregnancy, physical activity, alcohol consumption, body mass index (BMI), menopausal status, BMI and menopausal status interaction, and hormone therapy use.

§Multivariable model was adjusted for age, race, age at menarche, parity, age at first full-term pregnancy, physical activity, alcohol consumption, BMI, and hormone therapy use.

in risk (HR = 1.35, 95% CI = 1.11 to 1.65), and being a former smoker was associated with a less dramatic, statistically nonsignificant increase in risk (HR = 1.11, 95% CI = 0.99 to 1.24). In contrast, among women with a family history of breast cancer, current smokers had a slightly elevated risk, although the increase was not statistically significant (HR = 1.19, 95% CI = 0.79 to 1.79), and former smokers showed no increase in risk (HR = 0.87, 95% CI = 0.69 to 1.10). The likelihood ratio test for interaction indicated that the risks estimated for smoking status were different ($P<.001$; data not shown) for women with and without a family history of breast cancer.

We further stratified these analyses by menopausal status and found that, among women without a family history of breast cancer, the risk associated with current smoking appeared to be limited to postmenopausal women (postmenopausal women: HR = 1.39, 95% CI = 1.10 to 1.75; pre-/perimenopausal women: HR = 0.94, 95% CI = 0.51 to 1.74). Among women with a family history of breast cancer, however, the hazard ratio among current smokers was elevated only among pre-/perimenopausal women, albeit with wide confidence intervals that included 1.0 (HR = 1.47, 95% CI = 0.52 to 4.13). The likelihood ratio tests for interaction indicated no statistically significant interactions between smoking status and menopausal status within either of these two groups (data not shown).

Discussion

In this large prospective analysis, we observed an elevated risk of breast cancer associated with active smoking that increased with smoking intensity and, to a lesser extent, duration. The association with intensity was present in both pre-/peri- and postmenopausal women, but the association with duration appeared to be limited to postmenopausal women. In contrast, we found no evidence of a relationship between household passive smoking exposure and breast cancer risk. Accounting for household passive smoking exposure when analyzing the association of active smoking with breast cancer risk did not substantially change the risk estimates.

Paradoxically, early studies of smoking and breast cancer seemed to suggest a positive association between breast cancer and passive, but not active, smoking *(50,51)*. Numerous investigators have speculated that the inconsistency in these early findings may have been caused by including passive smokers in the unexposed referent category when examining the effects of active smoking *(9,10,13,40,43)*. In our analyses of active smoking, however, the exclusion of passive smokers from the unexposed referent group did not substantially affect the risk estimates for active smoking. This finding is not surprising, given the null findings for passive smoking. More recent reviews of the passive smoking literature *(11)* have concluded that there is a possible positive association between passive smoking and breast cancer, but there remains considerable inconsistency in findings, even among studies that have used quantitative exposure measures *(9,10,40)*.

Our passive smoking analysis was limited to household sources and did not include quantitative measures of intensity or duration. More detailed information on passive smoking, including quantitative measures of exposure in household, workplace, and social settings, was collected after the baseline survey. Initial analyses of these data *(52)* show that, among this cohort of women, household spousal sources of exposure comprised the primary source of all passive smoking exposures until the 1980s. Although these data will constitute the basis for a future, more detailed analysis of passive smoking exposures, this preliminary assessment suggests that the crude measures of passive smoking used in the analysis presented here likely captured the majority of lifetime passive exposures, although they may have inadequately estimated more recent passive exposures. Nonetheless, most literature on this topic has used passive smoking from household sources to estimate passive smoking exposures.

In contrast to earlier studies *(53–59)*, more recent studies *(26,30,33,42,60)* have provided increasing evidence of a positive association between active smoking and breast cancer. One of the most current literature reviews on this topic, published in 2002 *(9)*, concluded that, although substantial inconsistencies in reported results persist, the preponderance of evidence to date, particularly among more recent and better-designed studies, suggests that active smoking may be associated with a small increase in risk. That review also suggests that the risk may be

limited to exposures of long duration and/or to exposures occurring before a first full-term pregnancy. The results of our study are generally consistent with this conclusion in that we found a statistically significant association between active smoking and breast cancer that increased with both intensity and duration of smoking. Furthermore, this association was limited to women who began smoking before age 20 and who smoked for at least 5 years before their first full-term pregnancy.

A recently published international pooled analysis of 53 studies examining alcohol and tobacco use and breast cancer *(16)* found that the association between smoking and breast cancer was substantially confounded by alcohol consumption so that when the analysis was limited to nondrinkers, no relationship was found between active smoking (ever or current) and breast cancer. In contrast, when we restricted our analyses to the 35 123 nondrinkers in our cohort (data not shown), current smokers continued to have an elevated risk of breast cancer (HR = 1.66, 95% CI = 1.15 to 2.40).

The association of smoking and breast cancer in relation to first full-term pregnancy was first examined in 1988 in a study of premenopausal women *(55)*, which found no clear association. More recently, an analysis of the Nurses' Health Study cohort *(31)* reported that women who smoked for at least 5 years before their first full-term pregnancy had an increased risk of breast cancer (odds ratio [OR] = 1.13, 95% CI = 0.99 to 1.26), with a risk estimate remarkably similar to the one generated in our analysis. By contrast, a recent case–control study in Germany *(60)* reported no increased risk associated with smoking before first pregnancy (OR = 0.92, 95% CI = 0.52 to 1.65). In a 1999 population-based case–control study in Massachusetts, Lash and Aschengrau *(35)* initially reported increased breast cancer risk associated with active smoking before a first pregnancy (OR = 5.6, 95% CI = 1.5 to 21.0). However, a follow-up study by the same authors that used a similar design and population *(61)* failed to replicate these findings.

Numerous studies *(9,26,27,29–32,35,42,54,55,57,58,60,62–65)* have examined the association between age at smoking initiation and breast cancer risk with inconsistent results. Because early age at smoking initiation is likely to be highly correlated with smoking for long durations, as well as with smoking before a first pregnancy, disentangling the independent effects of smoking initiation at an early age can be problematic, and it was something we could not adequately examine in our analyses due to the high degree of collinearity between these variables.

In general, our results were similar for pre-/peri- and postmenopausal women. The only statistically significant effect modification we observed in our data was the stronger association between breast cancer risk and active smoking among women without a family history of breast cancer than among women with such a history. Statistical tests for interaction, however, are not particularly powerful, and some of our subgroup analyses, although hindered by small numbers, are somewhat provocative. When we limited our analysis to women without a family history of breast cancer, current smoking was associated with an increased risk of breast cancer only among postmenopausal women. Conversely, among women with a family history of breast cancer, there was no association with current smoking among postmenopausal women but there was a statistically nonsignificant increase in risk among pre-/perimenopausal women. An earlier study *(39)* also reported an interaction between family history of breast cancer and smoking, although in that study there was a stronger smoking effect among women with familial risk of breast cancer. That study, however, did not report risk estimates by menopausal status. This avenue of research warrants further study.

There are several limitations to our study. One is that we based women's active smoking status on their smoking status at the time they joined the CTS cohort (1995/1996), and we do not know how many women changed their smoking status or behavior during the 5 years of follow-up. Given the relatively older age structure of the cohort, however, it seems unlikely that many nonsmoking cohort members would have begun smoking during the follow-up period. If any changes in smoking behavior occurred, it is more likely that smokers quit. However, based on retrospective CTS data, it appears unlikely that a large percentage of women would have quit smoking within the 5 years of this study. Approximately 9.8% of the women who were former smokers on entering the cohort reported quitting within the previous 5 years. Thus, although our inability to account for changes in smoking status during the follow-up period may have caused some exposure misclassification, the effect is likely to be minimal. Furthermore, the elevated risks we found were strongest for current smokers and were not apparent in former smokers. Therefore, women who quit smoking during the study and were incorrectly classified as current smokers would bias our results for current smoking toward the null.

Our analysis examined risks associated with a number of tobacco exposure metrics and several strata of interest. Because of the large number of resulting comparisons, we cannot discount the possibility that some of our statistically significant results may be due to chance. However, the overall pattern of elevated risks associated with longer-term chronic exposures seems more consistent with probable causation than with chance.

Finally, the risk estimates generated by our analysis are fairly modest, and we cannot fully discount the possibility of residual confounding. The covariates included in our analysis, however, were specified in some detail and included a broad range of breast cancer risk factors. Two variables of potential importance that were not included were mammography use and age at menopause. However, mammography screening is nearly universal in this cohort of women, with remarkably little variability *(44)*. Therefore, it is unlikely that the risk estimates provided here were confounded by differences in mammography use. Unfortunately, data on cohort members' age at menopause was not yet available at the time we were conducting our analysis. There is some evidence that smoking is associated with an earlier age of menopause *(23)*, and earlier menopausal age is associated with decreased breast cancer risk *(66)*. Hence, adjusting our models for this covariate would likely increase our estimates of smoking-related risk.

Our study also has a number of strengths. The prospective design of this cohort analysis circumvents problems of recall and selection biases common to case–control studies. With approximately 2000 cases identified during follow-up, more than half of which occurred in never-smoking women, this study provides very good statistical power to examine risks associated with passive smoking. Additionally, because the CTS cohort was designed to study breast cancer, we have extensive information on many important potential confounding variables and effect modifiers, such as menopausal status and family history of breast

cancer. Although we did not explore gene–environment interactions, a number of preliminary results indicate that breast cancer risk associated with tobacco exposures is likely to be modified by polymorphisms in genes whose products are responsible for tobacco metabolism *(67–75)*. Particularly intriguing is the recent finding by Chang-Claude et al. *(72)*, suggesting that polymorphisms in the N-acetyltransferase 2 (NAT2) gene may act differentially in modifying breast cancer risk associated with exposures to active and passive smoking. That study reported that active smoking was associated with increased breast cancer risk among slow acetylators but not among rapid acetylators, whereas passive smoking was associated with a higher risk in both rapid and slow acetylators, although the effect was stronger and only statistically significant among the rapid acetylators.

Evaluating our results in the context of current literature is difficult, given the widely inconsistent results published to date. Although our results confirm those of some earlier studies *(26,30,31,33,35,42,60)*, they contradict the findings of others *(16,50,51,53,59–61)*. Heterogeneity in genetic susceptibility across study populations may explain some of the inconsistencies reported in the literature. Research into how genetic polymorphisms influence breast cancer risk associated with tobacco exposures holds great promise in adding to our understanding of this issue. Plans are under way to collect genetic information on the CTS cohort in the future that will allow us to evaluate this issue.

Our results, which suggest that active smoking may be associated with an increased risk of breast cancer, argue for further research that can account for heterogeneity in individual susceptibility. Exposures to tobacco smoke, if causally related to breast cancer, could offer one of the few available modifiable avenues for preventing this disease.

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