A Prospective Study of Smoking and Risk of Breast Cancer in Young Adult Women

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Abstract

Objective: To investigate the association between smoking and invasive breast cancers characterized by their estrogen receptor status in a large prospective study of mainly premenopausal women. Method: 112,844 women aged 25–42 years in 1989 were followed 10 years; questionnaire information on medical illnesses and risk factors was collected biennially and information on diet was collected in 1991 and 1995. During this period of follow-up (1,077,536 person-years), 1009 incident breast cancer cases were documented. Results: In the multivariate-adjusted models, smoking status was not significantly related to overall breast cancer risk: compared with never smokers, the relative risks (RRs) were 1.18 [95% confidence interval (CI) 1.02–1.36] for past smokers and 1.12 (95% CI 0.92–1.37) for current smokers. Increasing duration of smoking before the first pregnancy was associated with a greater risk of breast cancer, although little increase was seen in the highest category: compared with never smokers, RRs were 1.42 (95% CI 1.10–1.83) for 15–19 years of smoking and 1.10 (95% CI 0.80–1.52) for ≥20 years of smoking (*P* for trend = 0.01). Smoking was related most strongly to the risk of estrogen receptor-positive breast cancers. For women who had smoked for ≥20 years, the RR of estrogen receptor-positive cancer was 1.37 (95% CI 1.07–1.74) and the RR of estrogen receptor-negative cancer was 1.04 (95% CI 0.71–1.53). For smoking before age 15, the RRs were 1.49 (95% CI 1.03–2.17) for estrogen receptor-positive cancer and 1.19 (95% CI 0.69–2.08) for estrogen receptor-negative cancer. Conclusion: Our results suggest that longer duration of smoking may be related to the risk of estrogen receptor-positive breast cancer but possibly less so for estrogen receptor-negative breast cancer. (Cancer Epidemiol Biomarkers Prev 2004;13(3): 398–404)

Introduction

Breast cancer is the leading cancer among women (1) and many risk factors have been identified as possible initiators or promoters of this cancer (2). The association between smoking and breast cancer has been investigated in numerous studies. A weakly increased risk has been seen in some (3–8) but not in others (9–14). Recent reviews and meta-analyses concluded that an overall risk is plausible but weak (15–18). A recent pooled analyses of 53 case-control studies showed no risk of smoking in relation to breast cancer (19). Many prospective cohort studies have assessed the association between smoking and breast cancer (6, 7, 12–14, 20–23), but only two (21, 23) examined breast cancer classified by their estrogen receptor status. In one of these studies (21) with 1788 breast cancer cases, smoking was positively associated with estrogen receptor-positive cases, but the other study by Manjer *et al.* (23) with 268 cases did not find such an association. Inconsistent results between smoking and estrogen receptor-positive breast cancer have been seen in case-control studies (9, 24–27), with some studies finding a positive association (25, 27) and others finding no association (9, 24, 26).

Vitamin A has been hypothesized to reduce the risk of breast cancer through regulation of cell growth, differentiation, and death (28); some carotenoids can be converted to retinol and most have antioxidant activity that could potentially reduce oxidative damage to DNA caused by smoking (29). A recent analyses from our cohort showed a protective effect of carotenoids and retinol against breast cancer only among smokers (30).

The aim of our analyses was to assess the association between smoking and breast cancer in a large cohort of relatively young women—the Nurses' Health Study II (NHSII). We categorized breast cancers by their estrogen receptor because tobacco smoke may have both anti-estrogenic and estrogen receptor-activating effects (8, 31). We carried out secondary analyses to assess the association between smoking and breast cancer among categories of carotenoids and vitamin A intake.

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Materials and Methods

The NHSII is a prospective cohort study that was established in 1989 when 116,671 nurses aged 25–42 completed a baseline questionnaire about their medical

histories and life-styles (32). Subsequent questionnaires, mailed every 2 years, have been sent to update information on risk factors and medical events. The protocol for the study was approved by the Human Research Committees of the Brigham and Women's Hospital and the Harvard School of Public Health (Boston, MA).

Population for Analyses. The above information was collected from 116,671 women aged 25–42 who enrolled in the NHSII in 1989. In this analysis, we excluded women with the diagnosis of breast or other cancers at baseline. As a result, 112,844 women were included and comprised the final population for analysis. For specific quantitative smoking analyses, such as the past or current number of cigarettes smoked, women who did not report the number of cigarettes that they smoked were not included. There was a high percentage of follow-up (92%) among our study population.

Smoking. Smoking history was recorded in 1989 and updated biennially. For active smokers, information was collected concerning the number of cigarettes they smoked and the age they started smoking. From this and other information, the following smoking variables were used in our analyses: smoking status (never, past, or current), age started smoking (<15, 15–19, or 20+ years), duration of smoking (<10, 10–14, 15–19, or 20+ years), and number of cigarettes/day by current or past smokers (1–4, 5–14, 15–24, or 25+ cigarettes/day). The amount smoked daily was also used for two other variables: number of cigarettes/day before the first pregnancy and number of cigarettes/day by women who started before age 20 and who started at or after age 20. Pack-years of smoking was used to assess cumulative exposure, calculated by multiplying the number of packs/day (1 pack = 20 cigarettes) by the number of years over which that amount was smoked (<10, 10–24, or 25+ pack-years).

Data on Other Risk Factors. Age at menarche and height were reported on the baseline questionnaire. Information on other risk factors, including parity, age at first birth, history of benign breast disease, family history of breast cancer in mother and/or sister, oral contraceptive use, and weight was reported on the baseline questionnaire and was updated every 2 years based on responses to the follow-up questionnaires. We also included data on recent alcohol consumption (within the past year), measured on the 1989 baseline questionnaire, as a covariate in models. On each questionnaire, we collected data on menopausal status and, where applicable, age at menopause. At baseline, only 2.4% of the women were postmenopausal, and only 79 cases of breast cancer (7.8% of total cases) in these analyses were postmenopausal. We adjusted for menopausal status in the statistical models. Data on dietary intake were collected by food frequency questionnaires in 1991 and updated in 1995. The questionnaire assesses average frequency of intake over the previous year. For each woman, we calculated caloric and nutrient intakes by multiplying the frequency that each food item was consumed by the caloric or nutrient content for the specified portion size and then adding these up. We asked about use of multivitamins in addition to the use of specific supplements.

Breast Cancer Cases. On the 1991, 1993, 1995, 1997, and 1999 questionnaires, women were asked if they had been diagnosed with breast cancer in the previous 2 years. For identified cases of breast cancer, we requested permission to obtain hospital records and pathology reports. Pathology reports were obtained for 89% of the case subjects, and of these, 98% confirmed the self-reported diagnosis of breast cancer. Only invasive cases were included. A physician blinded to the exposure status of participants reviewed the medical records and abstracted information on estrogen and progesterone receptor status of breast cancer cases. Progesterone receptor status was highly associated with estrogen receptor status (*i.e.*, most estrogen receptor-positive cancers were also progesterone receptor-positive cancers and vice versa) and we therefore only show the data for estrogen receptor status. The few reported cases whose records failed to confirm breast cancer were excluded from analyses. However, because the degree of self-reporting accuracy was high, we included self-reported cases from whom records could not be obtained.

Statistical Analyses. We used multivariate Cox proportional hazards regression to model the risk of being diagnosed with breast cancer over the 10-year follow-up period (1989–1999) for each of the smoking variables stratified by age. Each participant contributed person-time of follow-up from the time the baseline questionnaire was returned in 1989 until the end of follow-up (June 1, 1999), the diagnosis of breast cancer, or death from any cause. Deaths in the cohort are reported by family members and the postal service or were detected by a search of the National Death Index for participants who have been lost to follow-up.

For covariates at baseline that remained constant throughout the duration of the study, such as age at menarche, cases and person-time of follow-up were assigned to the exposure level observed at baseline in 1989. For time-varying covariates, such as current oral contraceptive use or parity, cases and person-time were reassigned every 2 years according to the updated exposure values reported on each of the biennial questionnaires. Smoking variables were updated every 2 years and included as time-dependent variables (excluding the age of starting to smoke). Incidence rates were calculated as the sum of the cases divided by the sum of person-time observed for each exposure level. Incidence rate ratios [relative risks (RRs)] for each smoking level were calculated by dividing the incidence rate in that level by the rate in the never smokers. In multivariate analyses, we adjusted for the following factors: age at menarche (<12, 12, 13, or ≥14 years), parity and age at first birth (nulliparous, parity 1–2 and age at first birth <25 years, parity 1–2 and age at first birth 25–29 years, parity 1–2 and age at first birth 30 years, parity ≥3 and age at first birth <25 years, or parity ≥3 and age at first birth ≥25 years), family history of breast cancer in mother and/or sister (yes or no), history of benign breast disease (yes or no), oral contraceptive use (never, past user with duration of use <4 years, past user with duration of use ≥4 years, current user with duration of use <8 years, or current user with duration of use ≥8 years), recent alcohol consumption (0, 0.1–4.9, 5.0–9.9, 10–19.9, or ≥20 average g/day), body mass index (BMI; <18.5, 18.5 to <20, 20 to <22.5, 22.5 to <25, 25 to

<30, or 30+ kg/m^2), height (50–61.9, 62–64.9, 65–67.9, or ≥68 in.), and menopause status (premenopause, postmenopause, or unsure). Because the models with and without the covariates produced similar results, we present only the results from multivariate-adjusted analyses. We present two-sided 95% confidence intervals (CIs) for all RRs. For trend analyses, we tested the significance of a continuous variable in the model where its first value represented never smokers and the other values represented the middle of the smoking category variable (*e.g.*, those who never smoked were set to 1, those who smoke 1–4 cigarettes were set to 2, those who smoked 5–14 cigarettes were set to 10, etc.).

We conducted secondary analyses of the association between smoking and breast cancer stratified by intakes of carotenoids and preformed vitamin A (retinol). The *P* value for the tests for interaction was obtained from a likelihood ratio test with 2 degrees of freedom.

Results

Table 1 shows the distribution of breast cancer risk factors by smoking status of women in our study at baseline. BMI, age, and family history of breast cancer did not vary by smoking status. However, consumption of carotenoids and vitamin A was lower among the current smokers. During 10 years of follow-up between 1989 and 1999, 1009 breast cancer cases were recorded among 112,844 women (1,077,536 person-years).

Using information updated during follow-up, there was no overall relation between smoking and overall risk of breast cancer (Table 2). No linear association was apparent with the number of cigarettes smoked by women according to their smoking status (current or past smokers; Table 2). No appreciable difference was seen for the overall risk of breast cancer according to the age that women started to smoke (<15, 15–19, or 20+ years). However, the association between duration of smoking before the first pregnancy and risk of breast cancer reached statistical significance (*P* for trend = 0.01), although the highest category (≥20 years of smoking) was not significantly associated with the risk (Table 2). These trends were not significant among smokers only. The number of pack-years of smoking was also not significantly associated with risk of breast cancer. Compared with never smokers, the RRs were 1.16 (95% CI 0.98–1.39) for women who smoked <10 pack-years, 1.16 (95% CI 0.97–1.38) for women who smoked 10–24 pack-years, and 1.13 (95% CI 0.86–1.50) for women who smoked ≥25 pack-years (*P* for trend = 0.2). We found similar results when using smoking variables at baseline (data not shown).

We carried out analyses of breast cancers characterized by the estrogen receptor status (Table 3). Most (83%) of the estrogen receptor-positive cancers were progesterone receptor-positive, and similarly, most (72%) of the estrogen receptor-negative cancers were progesterone receptor-negative. For estrogen receptor-positive breast cancer, we observed a statistically significant association (*P* for trend = 0.04) between the number of cigarettes/day before age 20 [RR for smoking ≥25 cigarettes 1.51 (95% CI 1.04–2.20) as compared with never smokers. The duration of smoking was also associated with risk of estrogen receptor-positive breast cancer. For those who smoked ≥20 years, the RR was 1.37 (95% CI 1.07–1.74), *P* for trend = 0.003 for estrogen receptor-positive cancer, and the RR was 1.04 (95% CI 0.71–1.53), *P* for trend = 0.7 for estrogen receptor-negative cancer (Table 3). The trends were not significant among smokers only. Finally, we found an increased risk of estrogen receptor-positive breast cancer among women who started smoking before age 15 [compared with never smokers RR 1.49 (95% CI 1.03–2.17) but not for estrogen receptor-negative cancer RR 1.19 (95% CI 0.69–2.08); Table 3]. Using the likelihood ratio test for interaction, we did not find a statistically significant interaction between estrogen receptor type and smoking variables in relation to total breast cancer.

We also stratified the associations between smoking variables and breast cancer risk by tertiles of vitamin A intake (retinol) and total and specific carotenoids intake (Table 4). For each of the smoking variables, there was a tendency of increased risk of breast cancer among women in the lowest tertiles compared with a tendency of null or negative risks among women in the highest tertiles. Total carotenoids and α- and β-carotene had mostly significant tests for interaction with the smoking variables.

Table 1. Age-adjusted characteristics of women in the NHSII according to smoking status at baseline (1989)

	Never (*n* = 74,068)	Past (*n* = 24,188)	Current (*n* = 15,054)
Mean values			
Age (yr)	34	35	34
BMI (kg/m^2)	24	24	24
Height (in.)	64.8	65.0	64.9
Age at first birth (yr)	25.6	25.8	24.5
Mean alcohol consumption (g/day)[a]	2.3	4.3	5.0
Carotenoids (IU/day)[a]	9027	9696	8267
Vitamin A (retinol; IU/day)[a]	3734	3840	3544
Prevalence			
Age at first menarche (<13 yr; %)	24	24	26
Parity (>2; %)	19	17	16
Oral contraceptive use (%)	13	12	13
Benign breast disease (%)	28	30	30
Family history of breast cancer (%)	9	9	9

[a]Calculated from a food frequency questionnaire in 1991.

Table 2. Multivariate-adjusted RR of developing breast cancer among women in the NHSII according to smoking exposure updated during follow-up

Smoking variables	No. cases	Person-years	RR	95% CI	*P* for trend
Current status					
Never smokers	596	704,023	1.00		
Past smokers	283	242,916	1.18	1.02–1.36	
Current smokers	128	125,138	1.12	0.92–1.37	
Never smokers	596	704,023	1.00		
1–4 cigarettes/day (current)	14	20,106	0.77	0.44–1.33	
5–14 cigarettes/day (current)	37	34,132	1.18	0.88–1.74	
15–24 cigarettes/day (current)	55	47,521	1.14	0.90–1.61	
25+ cigarettes/day (current)	20	20,308	0.98	0.69–1.70	0.4
Never smokers	596	704,023	1.00		
1–4 cigarettes/day (past)	66	60,604	1.21	0.94–1.56	
5–14 cigarettes/day (past)	94	74,329	1.32	1.06–1.65	
15–24 cigarettes/day (past)	76	70,854	1.04	0.82–1.33	
25+ cigarettes/day (past)	45	35,835	1.12	0.82–1.53	0.6
Duration of smoking					
Never smokers	596	704,023	1.00		
<10 years	52	54,354	1.14	0.85–1.52	
10–14 years	99	103,359	1.19	0.96–1.48	
15–19 years	96	101,687	1.06	0.85–1.33	
20+ years	166	114,113	1.21	1.01–1.45	0.04
Age started smoking					
Never smokers (at baseline: 1989)	603	707,686	1.00		
<15 years	55	53,531	1.29	0.97–1.71	
15–19 years	203	200,616	1.09	0.93–1.29	
20+ years	148	115,703	1.18	0.97–1.42	
Smoking duration before first pregnancy					
Never smokers	596	704,023	1.00		
1–4 years	39	38,704	1.02	0.72–1.44	
5–9 years	112	104,816	1.12	0.91–1.39	
10–14 years	119	113,502	1.19	0.97–1.47	
15–19 years	80	64,447	1.42	1.10–1.83	
20+ years	49	35,766	1.10	0.80–1.52	0.01

Note: Covariates: stratified by age and further adjusted for BMI, height, oral contraceptives, parity and age at first birth, age at menarche, family history of breast cancer, benign breast disease, alcohol consumption, and menopause status.

Discussion

Our analyses of smoking and breast cancer risk among women in the NHSII suggest a positive relation with estrogen receptor-positive, but not estrogen receptor-negative, breast cancers. This association was consistent for several smoking variables. Smoking at an earlier age and for a longer duration appears more likely to increase the risk of estrogen receptor-positive cancer.

The cohort design avoids recall bias, which is a major concern for case-control studies. Furthermore, the measurement of smoking was updated biennially, allowing us to minimize measurement error from changes in smoking behavior during follow-up. Our study population was relatively young (25–42 years at baseline). Because most of the women in our study were premenopausal, our results are most applicable to this group of women. However, a review of the available data on the relation of smoking and overall risk of breast cancer among premenopausal and postmenopausal women shows no significant difference (18, 22). We cannot exclude the possibility of a modest positive association between smoking and estrogen receptor-negative breast cancer because the number of such cases was limited even in this large cohort. Although there was a higher risk for smokers to develop estrogen receptor-positive breast cancer compared with estrogen receptor-positive breast cancer, this difference did not reach statistical significance as assessed by likelihood ratio test for interaction. However, this test has low power to detect moderate interactions. Furthermore, in the original NHS, there was a similar effect modification by estrogen receptor type among heavy smokers (20). We found no appreciable difference in the proportion of women who had a screening mammography according to their receptor status or smoking history, which suggests that there was no serious detection bias.

In this cohort, we did not have information on passive smoking, which was recently suggested by others to increase the risk of breast cancer (4, 33, 34). Passive smokers might have been included in the never smokers group in our study, and if passive smoking increases breast cancer risk, this would attenuate the observed association between smoking and breast cancer. However, a recent analysis of the NHS (22) and an earlier cohort study (35) failed to find an association between passive smoking and risk of breast cancer.

One other large cohort assessed the association between smoking and breast cancer risk subdivided by estrogen receptor status and found similar results (21). London *et al.* (21) observed a RR of 1.38 (95% CI 1.04–1.84) for estrogen receptor-positive breast cancer among women participating in the original NHS who smoked ≥25 cigarettes/day. However, a clear positive trend was not seen across all smoking categories. The only other prospective cohort study that assessed the

association between smoking and breast cancer (categorized by estrogen receptor status of the cancer) found an increased risk of estrogen receptor-negative breast cancer but failed to find an association among women with estrogen receptor-positive breast cancer (23). The RR for current smokers compared with never smokers was 2.21 (95% CI 1.23–3.96) for estrogen receptor-negative breast cancer and 0.88 (95% CI 0.63–1.22) for estrogen receptor-positive breast cancer (23). The latter study was relatively small (n = 268 cases of breast cancer) and smoking behavior and covariates were only assessed at baseline and were not updated during follow-up. Updating the exposure status is an advantage of cohort studies because this minimizes misclassification caused by the change in smoking habits.

In the other cohort studies, when cases were not subdivided by estrogen receptor status, no overall association between smoking and incidence of breast cancer was found (12–14, 20, 22), which is compatible with our findings for the overall association (not categorized by estrogen receptor status) between smoking and breast cancer. Only two large cohort studies found a positive association between smoking and breast cancer risk. In a cohort involving 2552 breast cancer cases with an average of 10.6 years of follow-up, Terry *et al.* (6) recently reported that only women who smoked for ≥40 years were at higher risk of breast cancer when compared with never smokers (RR 1.37; 95% CI 1.15–1.62). We were not able to investigate such a long latency period because of the relatively young age of our study population. The other large cohort that found a positive relation between intensity and duration of smoking and breast cancer used breast cancer mortality instead of incidence (7). The mortality end point does not differentiate between an etiological and a prognostic effect of smoking (*e.g.*, smokers may have had late treatment and/or more aggressive cancer than nonsmokers).

Carotenoids and vitamin A intake may protect against breast cancer (28, 29). In one study with 1589 cases of breast cancer, α- and β-carotene seemed to protect against breast cancer, but only among smokers (36). This was also found by a recent analyses from our cohort (30). Our results support a possible protective effect of vitamin A and carotenoids among women who smoke in that the smoking variables were less associated with breast cancer among women with higher intake. This apparent protective effect may be related to the role of vitamin A in cell differentiation. Russo *et al.* (37) have shown in animals that breast carcinogens have much less effect after cell differentiation due to a first pregnancy. This is consistent with our findings of an increased risk of estrogen receptor-positive breast cancer among women who smoked prior to their first pregnancy.

An increased risk of breast cancer among smokers may be due to carcinogens contained in tobacco smoke such as polycyclic aromatic hydrocarbons (PAH), aromatic amines, and nitrosamines. PAHs are thought to exert their carcinogenic effect when metabolized in breast tissue into active intermediates that form DNA adducts and cause mutations (38). Additionally, PAH may induce

Table 3. Multivariate-adjusted RR of breast cancer characterized by estrogen receptor status according to updated smoking exposure among women in the NHSII

Smoking variables	Estrogen receptor-positive breast cancer				Estrogen receptor-negative breast cancer			
	No. cases	RR	95% CI	P for trend	No. cases	RR	95% CI	P for trend
Never smokers	302	1.00			152	1.00		
1–4 cigarettes/day (current)	11	1.41	0.79–2.52		1	0.22	0.03–1.16	
5–14 cigarettes/day (current)	20	1.22	0.75–2.00		9	1.14	0.58–2.24	
15–24 cigarettes/day (current)	27	1.16	0.78–1.71		14	1.30	0.75–2.27	
25+ cigarettes/day (current)	10	0.81	0.43–1.53	0.5	7	1.41	0.65–3.3	0.4
Never smokers	302	1.00			152	1.00		
1–4 cigarettes/day (past)	41	1.46	1.05–2.03		15	1.07	0.63–1.83	
5–14 cigarettes/day (past)	56	1.55	1.16–2.07		20	1.14	0.71–1.82	
15–24 cigarettes/day (past)	38	0.98	0.69–1.40		21	1.18	0.74–1.87	
25+ cigarettes/day (past)	30	1.49	1.01–2.19	0.2	7	0.71	0.33–1.53	0.9
Duration of smoking								
Never smokers	302	1.00			152	1.00		
<10 years	28	1.17	0.78–1.75		10	0.85	0.44–1.61	
10–14 years	57	1.33	0.99–1.78		30	1.40	0.94–2.08	
15–19 years	57	1.26	0.94–1.70		20	0.88	0.55–1.41	
20+ years	95	1.37	1.07–1.74	0.003	34	1.04	0.71–1.53	0.7
Age started smoking								
Never smokers (at baseline: 1989)	306	1.00			153	1.00		
<15 years	32	1.49	1.03–2.17		14	1.19	0.69–2.08	
15–19 years	120	1.29	1.04–1.60		42	0.90	0.63–1.27	
20+ years	81	1.24	0.96–1.60		37	1.28	0.89–1.85	
Smoking duration before first pregnancy								
Never smokers	302	1.00			152	1.00		
1–4 years	21	1.05	0.65–1.69		8	0.86	0.41–1.81	
5–9 years	69	1.31	0.99–1.73		27	1.10	0.72–1.69	
10–14 years	70	1.47	1.11–1.93		28	1.12	0.73–1.70	
15–19 years	45	1.50	1.06–2.12		19	1.27	0.76–2.13	
20+ years	27	1.17	0.76–1.79	0.003	7	0.69	0.31–1.52	0.8

Notes: Covariates: stratified by age and further adjusted for BMI, height, oral contraceptives, parity and age at first birth, age at menarche, family history of breast cancer, benign breast disease, alcohol consumption, and menopause status.

Table 4. Multivariate-adjusted RR of breast cancer in relation to updated smoking exposure variables stratified by vitamin A (retinol) and carotenoid tertiles (cumulative update of nutrients in 1991 and 1995)

Smoking variable	Vitamin A (retinol) tertiles (IU/day)			Total carotenoids tertiles (IU/day)		
	1 (<1749)	2 (1749–3829)	3 (>3829)	1 (<6074)	2 (6068–10,167)	3 (>10,167)
Never smokers (reference)	1.00	1.00	1.00	1.00	1.00	1.00
Years of smoking						
<10	0.91	1.51	1.38	1.39	1.61	0.87
10–14	1.47	1.23	1.05	1.38	1.59	0.94
15–19	1.24	0.58	1.43	1.23	1.16	0.92
20+	1.29	1.28	1.01	1.68	1.30	0.78
P for trend	0.04	0.6	0.4	0.003	0.07	0.2
P for interaction			0.08			0.03
Never smokers (reference)	1.00	1.00	1.00	1.00	1.00	1.00
No. cigarettes for current smokers						
1–4	0.39	1.17	0.89	1.61	1.35	0.62
5–14	1.43	1.47	1.06	2.02	0.55	1.08
15–24	1.68	0.77	0.98	1.62	1.33	0.61
25+	1.45	1.35	0.19	1.05	1.01	0.72
P for trend	0.02	0.7	0.2	0.2	0.8	0.2
P for interaction			0.4			0.08
Never smokers (reference)	1.00	1.00	1.00	1.00	1.00	1.00
No. cigarettes for past smokers						
1–4	1.91	1.46	0.39	0.91	2.08	0.82
5–14	1.38	1.34	1.32	1.72	1.43	0.94
15–24	1.23	0.80	1.20	1.23	1.22	0.93
25+	1.29	0.83	1.47	1.46	1.59	1.03
P for trend	0.2	0.5	0.2	0.1	0.1	1.0
P for interaction			0.6			0.1
Never smokers (reference)	1.00	1.00	1.00	1.00	1.00	1.00
Age at first smoking						
<15	1.35	1.35	1.59	1.50	1.96	0.94
15–19	1.16	1.03	1.12	1.31	1.20	0.88
20+	1.41	1.17	0.96	1.56	1.32	0.86
P for interaction			0.7			0.05
	α-carotene tertiles (mg/day)			β-carotene tertiles (mg/day)		
	1 (<432)	2 (432–819)	3 (>819)	1 (<2902)	2 (2902–4712)	3 (>4712)
Never smokers (reference)	1.00	1.00	1.00	1.00	1.00	1.00
Years of smoking						
<10	1.20	1.91	0.76	1.52	1.48	0.92
10–14	1.26	1.54	0.93	1.44	1.41	1.03
15–19	1.13	1.26	0.84	1.32	1.24	0.80
20+	1.50	1.27	0.81	1.77	1.10	0.87
P for trend	0.02	0.07	0.2	0.001	0.3	0.3
P for interaction			0.05			0.06
Never smokers (reference)	1.00	1.00	1.00	1.00	1.00	1.00
No. cigarettes for current smokers						
1–4	0.64	1.10	0.49	0.77	0.67	0.69
5–14	1.56	1.60	0.74	2.13	0.77	1.23
15–24	1.74	1.01	0.70	1.90	1.20	0.58
25+	0.94	0.98	1.25	1.23	0.72	1.22
P for trend	0.2	1.0	0.9	0.07	0.8	0.9
P for interaction			0.3			0.1
Never smokers (reference)	1.00	1.00	1.00	1.00	1.00	1.00
No. cigarettes for past smokers						
1–4	1.14	1.85	0.82	1.40	1.98	0.63
5–14	1.81	1.45	0.87	2.23	1.63	0.79
15–24	0.89	1.26	0.98	1.12	0.82	1.14
25+	1.43	1.44	1.83	1.19	1.25	1.14
P for trend	0.3	0.2	0.6	0.2	0.8	0.6
P for interaction			0.1			0.001
Never smokers (reference)	1.00	1.00	1.00	1.00	1.00	1.00
Age at first smoking						
<15	1.19	2.12	0.85	1.75	1.79	0.89
15–19	1.30	1.14	0.87	1.34	1.19	
20+	1.41	1.35	0.83	1.84	0.97	0.86
P for interaction			0.02			0.03

*P*450 enzymes that catabolize estrogens into genotoxic catechol estrogen metabolites (39). This carcinogenic effect is believed to be dependent on the stage of mammary tissue differentiation; the less differentiated the mammary tissue, the more effective these compounds are in inducing cancer (8, 40–42), which may explain the stronger effect of smoking at a younger age. Tobacco has also been hypothesized to protect against breast cancer by inhibiting the aromatization of androgens into estrogens (43). Band *et al.* (8) suggested that this protective effect is limited to postmenopausal rather than premenopausal women and therefore indirectly supporting our findings of nonprotective effects of smoking among mostly premenopausal women.

In conclusion, our results among mainly premenopausal women suggest that smoking is a risk factor for estrogen receptor-positive breast cancer; but for estrogen receptor-negative breast cancer, the risk was less clear and statistically nonsignificant. Given the large number of women exposed to tobacco smoke, this may be an important finding for efforts to minimize the growing incidence of breast cancer among women worldwide. Our findings suggest that breast cancer should be characterized by estrogen receptor status in future studies that examine the effect of smoking.

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