Cigarette Smoking and the Incidence of Breast Cancer

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Background: Tobacco smoke contains carcinogens, which may increase the risk of breast cancer (BC). Conversely, cigarette smoking also has antiestrogenic effects, which may reduce the risk of BC. The association between smoking and BC remains controversial.

Methods: Prospective cohort study of 111 140 participants of the Nurses' Health Study from 1976 to 2006 for active smoking and 36 017 women from 1982 to 2006 for passive smoking.

Results: During 3 005 863 person-years of follow-up, 8772 incident cases of invasive BC were reported. After adjustment for potential confounders, the hazard ratio (HR) of BC was 1.06% (95% confidence interval [CI], 1.01%-1.10%) for ever smokers relative to never smokers. Breast cancer incidence was associated with a higher quantity of current (*P* for trend = .02) and past (*P* for trend = .003) smoking, younger age at smoking initiation (*P* for trend = .01), longer duration of smoking (*P* for trend = .01), and more pack-years of smoking (*P* for trend = .005). Premenopausal smoking was associated with a slightly higher incidence of BC (HR, 1.11; 95% CI, 1.07-1.15 for every increase of 20 pack-years), especially smoking before first birth (1.18; 1.10-1.27 for every increase of 20 pack-years). Conversely, the direction of the association between postmenopausal smoking and BC was inverse (0.93; 0.85-1.02 for every increase of 20 pack-years). Passive smoking in childhood or adulthood was not associated with BC risk.

Conclusion: Active smoking, especially smoking before the first birth, may be associated with a modest increase in the risk of BC.

Arch Intern Med. 2011;171(2):125-133

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BREAST CANCER (BC) IS THE most common cancer to affect women worldwide.[1] The annual incidence ranges from 11.8 per 100 000 women in Eastern China to 86.3 per 100 000 in North America,[2] suggesting the influence of environmental or lifestyle factors in the etiology of BC. Tobacco smoking is one of the leading preventable risk factors of cancer in respiratory and nonrespiratory sites.[3,4] Tobacco smoke contains potential human breast carcinogens, including polycyclic aromatic hydrocarbons, aromatic amines, and *N*-nitrosamines.[3,5-7] Carcinogens in tobacco pass through the alveolar membrane and enter the bloodstream[8] and are transported to mammary tissue through plasma lipoproteins.[9,10] Metabolites of cigarette smoke have been detected in nonlactating cigarette smokers in breast fluid obtained through standard nipple aspiration techniques.[11,12] Furthermore, because these breast carcinogens are lipophilic, they may be stored in breast adipose tissue and metabolized and activated by mammary epithelial cells.[13,14] Conversely, smoking has been postulated to have an antiestrogenic effect,[15] which may be associated with a lower risk of BC. The antiestrogenic effect of smoking has been supported by an increased risk of osteoporosis,[16,17] an early age at natural menopause,[18] and attenuated effects of hormone therapy (HT) among smokers.[16]

Numerous epidemiologic studies[13] have been conducted on the association between cigarette smoking and BC risk, and results from these studies have inconsistently suggested positive, inverse, or null associations. The direction and magnitude of the overall association between cigarette smoking and BC may differ according to the hormonal profile and other characteristics of the study population. Lifetime smoking exposure consists of many facets, including active and passive smoking, as well as quantity, duration, cessation, and age at initiation of smoking, which are difficult to assess accurately. In case-control studies, recall bias must be considered.

Our group previously reported a slightly elevated relative risk of BC among active but not passive smokers from the Nurses' Health Study based on follow-up from 1982 to 1996 that included 3140 cases of BC, especially when smoking was initi-

Corrected on March 22, 2011

ated at a young age.[19] We present herein an updated analysis that includes follow-up from 1976 to 2006 and adds 5632 incident cases, with assessment of the potential effect of multiple measures of active and passive smoking and of smoking during various reproductive periods.

METHODS

The Nurses' Health Study is a large prospective cohort established in 1976. At baseline, 121 700 married female nurses aged 30 to 55 years and living in the 11 most populous states in the United States responded to a mailed questionnaire inquiring about their health status, lifestyle factors, and demographic characteristics. Since 1976, each participant has been mailed a questionnaire biennially to update information on demographic, anthropometric, and lifestyle factors and newly diagnosed diseases.

The analysis on active smoking was restricted to 111 140 women who did not have prevalent invasive or in situ BC or other cancers and who provided information on smoking in 1976. Because questions on passive smoking were not asked until 1982, the follow-up for passive smoking analysis started in 1982. The analysis on passive smoking was restricted to 36 017 women who did not have prevalent invasive or in situ BC or other cancers, who never smoked, and who provided information on passive smoking in 1982. All included women were followed up biennially from cohort entry (1976 for active smoking analysis and 1982 for passive smoking analysis) until the earliest of the following events: diagnosis of invasive or in situ BC, loss to follow-up, death, or the end of the study period in 2006. Women who were lost to follow-up in each cycle were not followed up for that cycle but could reenter the analysis if they responded to the next questionnaire. To eliminate the effect of active smoking in the analysis on passive smoking, the follow-up also ended when women started smoking. The follow-up rate (calculated as eligible person-years divided by the maximum possible number of person-years and assuming no loss to follow-up) was 82.5% for the active smoking analysis and 89.0% for the passive smoking analysis. This study was approved by the institutional review board of the Brigham and Women's Hospital.

ASSESSMENT OF CIGARETTE SMOKING

The status and quantity of current smoking were first assessed in 1976 and updated biennially. Past smoking status and quantity were asked only once in the 1976 questionnaire. In 1976, current and past smokers were also asked about the age at which they started smoking, whether they had ever quit smoking for 6 months or longer, and the age at which they quit smoking. Questions related to passive smoking, including parental smoking status when living with them, the number of years they lived with a smoker in adulthood, and the status and frequency of exposure to cigarette smoke at home and work, were asked in 1982.

Duration of smoking was derived by deducting the age at which they started smoking from their current age for current smokers and from the age at which they quit smoking for past smokers. For past smokers, the number of years since quitting was calculated as the difference between current age and the age at which they quit smoking. Duration of smoking for current smokers and years since quitting were updated biennially. Pack-years of smoking was derived by multiplying the number of packs per day (1 pack = 20 cigarettes) and the number of years during which that quantity was smoked. Pack-years of smoking from menarche to first birth, from first birth to menopause, and after menopause were derived from updated information on the age at which they started and stopped smoking and the amount of current and past smoking.

ASCERTAINMENT OF BC

Participants were asked biennially whether they had been diagnosed as having BC during the past 2 years and, if so, to report the date of diagnosis. Deaths were reported by next of kin or by the US Postal Service in response to the follow-up questionnaires. The National Death Index was also routinely searched for deaths among women who did not respond to the questionnaires. All women who reported new onset of BC were asked for permission to review their relevant medical records. Study physicians reviewed all medical records and pathology reports to confirm disease status and tumor details, including hormone receptor status and invasiveness. In the present study, we included invasive BC confirmed by medical record or by the nurses themselves because self-reports of BC have been found to be highly reliable.[20] Medical record–adjudicated cases of BC account for 88.0% and 87.7% of all included cases for the analysis on active and passive smoking, respectively.

ASSESSMENT OF OTHER COVARIATES

Participants in the Nurses' Health Study were asked biennially about their reproductive factors, anthropometric characteristics, lifestyle, and diagnosis of other diseases. Current body mass index (BMI) and BMI at age 18 years were calculated as weight in kilograms divided by height in meters squared, using weight at the respective age and height in adulthood. Assessment of age, parity, current weight, alcohol consumption, physical activity, oral contraceptive use, menopausal status, age at menopause, HT use, history of benign breast disease, and family history of BC were updated during follow-up.

STATISTICAL ANALYSIS

A Cox proportional hazards regression model was used to assess the association between active and passive smoking and the incidence of BC. Active smoking was analyzed as smoking status, quantity of smoking, age at which participants started smoking, duration of smoking, years since quitting smoking, and pack-years of smoking in defined categories. Passive smoking was analyzed as exposure to parental smoking when living with them, passive smoking at work, passive smoking at home, and the number of years participants lived with someone who smokes in defined categories. We also derived an index of passive smoking that integrates frequency and years of exposure. All categorical variables of active and passive smoking were used as indicator variables, with the lowest level as the reference. Trend tests for categorical measures of smoking were based on the midpoint value of each category.

Potential confounding factors included age, family history of BC among first-degree relatives, age at menarche, height, BMI at age 18 years, oral contraceptive use, history of benign breast disease, leisure-time physical activity, alcohol consumption, a derived variable cross-stratifying age at first birth by parity, current BMI, age at menopause, menopausal status, and HT use. Updated history of mammogram screening and types of HT (estrogen, progesterone, or combined) were also considered as potential confounders, but the adjustment for them did not substantially change the results. Passive smoking status at work and at home was also adjusted for in the analysis on active smoking. Active smoking status was additionally adjusted for in the analysis of the quantitative smoking measures (quantity, age started, duration, and pack-years). Because smoking cessation is related to weight gain,[21] which may increase the risk of BC for postmenopausal women,[1] the potential effect modification of number of cigarettes a day when respondents started and stopped smoking by changes in BMI was assessed by stratified

Table 1. Age-Standardized Distribution of Selected Personal Characteristics of Person-years of Follow-up According to Active and Passive Smoking Status[a]

	Active Smoking			Passive Smoking		
Personal Characteristic	Never	Past	Current	Never	Occasionally	Regularly
Age, mean, y	56.3	58.2	52.4	59.6	59.4	59.1
Family history, %	15.0	15.9	14.5	15.7	15.7	15.6
History of benign breast disease, %	48.2	51.4	44.2	49.1	50.2	49.6
Nulliparous, %	6.8	6.6	7.3	6.4	6.3	7.2
Parous						
No. of children, mean	3.2	3.1	3.2	3.1	3.2	3.2
Age at first birth, mean, y	24.9	24.8	24.7	25.2	24.8	24.6
BMI, mean	25.8	25.9	24.4	25.5	26.0	26.8
BMI at age 18 y, mean	21.1	21.4	21.6	21.0	21.1	21.2
Postmenopausal, %	63.6	64.5	68.3	75.0	74.7	75.1
Used oral contraceptives, %	46.2	51.9	46.6	46.1	46.9	48.5
Alcohol consumption, mean, g/d	3.6	6.8	8.6	3.3	3.7	3.4

Abbreviation: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared).
[a]At the 1976 baseline, 111 140 participants in the Nurses' Health Study were included in the analysis of active smoking. At the 1982 baseline, 36 017 participants in the Nurses' Health Study were included in the analysis of passive smoking.

Table 2. Smoking Status and Pack-years of Smoking in Relation to Incidence of Breast Cancer Among 111 140 Participants in the NHS With Follow-up From 1976 to 2006

			Hazard Ratio (95% Confidence Interval)		
Smoking Status	No. of Person-years	No. of Cases	Age-Adjusted	Covariate-Adjusted I[a]	Covariate-Adjusted II[b]
Smoking status					
Never	1 341 442	3788	1 [Reference]	1 [Reference]	1 [Reference]
Ever	1 664 421	4984	1.07 (1.03-1.12)	1.06 (1.01-1.10)	1.07 (1.02-1.12)
Current	586 952	1422	1.02 (0.96-1.09)	1.05 (0.98-1.12)	1.09 (1.02-1.17)
Past	1 077 469	3562	1.09 (1.04-1.14)	1.06 (1.01-1.11)	1.06 (1.01-1.11)
Total smoking after menarche, pack-years					
0	1 341 442	3788	1 [Reference]	1 [Reference]	1 [Reference]
1-10	528 586	1419	1.03 (0.97-1.09)	1.00 (0.94-1.07)	1.00 (0.94-1.07)
11-20	418 217	1155	1.08 (1.02-1.16)	1.07 (1.00-1.14)	1.08 (1.01-1.16)
21-30	330 255	949	1.03 (0.96-1.10)	1.04 (0.97-1.12)	1.07 (1.00-1.15)
31-40	205 490	713	1.10 (1.02-1.19)	1.12 (1.03-1.21)	1.16 (1.07-1.26)
41-50	108 847	365	0.98 (0.88-1.09)	1.01 (0.90-1.12)	1.05 (0.94-1.18)
≥51	90 966	365	1.11 (1.00-1.24)	1.14 (1.02-1.28)	1.19 (1.07-1.33)
P for trend			.04	.005	<.001
Every increase of 20 pack-years			1.03 (1.01-1.06)	1.04 (1.01-1.07)	1.06 (1.03-1.09)

Abbreviation: NHS, Nurses' Health Study.
[a]Adjusted for age, family history of breast cancer, age at menarche, height, body mass index at age 18 years, oral contraceptive use, history of benign breast disease, leisure-time physical activity, alcohol consumption, passive smoking at home and at work, age at first birth, parity, and current body mass index.
[b]Additionally adjusted for age at menopause, menopausal status, and postmenopausal hormone use.

analyses, and the significance of effect modification was evaluated. The potential heterogeneity in the association between smoking and BC across various reproductive periods was assessed using a fixed-effects meta-analysis of effect estimates derived from each period weighted by the inverse variance. Polychotomous logistic regression software[22] was used to test the heterogeneity of the association between smoking and subtypes of BC according to tumor estrogen receptor (ER) and progesterone receptor (PR) status.

RESULTS

A total of 8772 incident cases of BC arose during 3 005 863 person-years of follow-up from 1976 to 2006. Relative to person-years with other smoking status, current smokers were more likely to be postmenopausal and to have a lower current BMI; past smokers were more likely to have a family history of BC, to have a history of benign breast disease, and to have ever used oral contraceptives; and never smokers tended to consume less alcohol (**Table 1**). A total of 2890 incident cases of BC occurred during 876 996 person-years of follow-up among never smokers from 1982 to 2006. Women with regular exposure to passive smoking had a higher BMI and were more likely to be nulliparous and to have used oral contraceptives.

Ever smokers had a marginally increased incidence of BC compared with never smokers, and the increase in incidence seemed to be comparable for past smokers and current smokers (**Table 2**). Every increase of 20 pack-years of smoking after menarche was associated with a marginal increase of incidence of BC after adjusting for

Table 3. Current and Past Amount of Smoking, Age One Started Smoking, Duration of Smoking, and Years Since Quitting in Relation to Incidence of Breast Cancer Among 111 140 Participants in the NHS With Follow-up From 1976 to 2006

	Person-years	No. of Cases	Hazard Ratio (95% Confidence Interval)	
			Age-Adjusted	Covariate-Adjusted[a]
Current amount of smoking, cigarettes/d				
Never smoker	1 341 442	3788	1 [Reference]	1 [Reference]
1-14	189 721	484	1.00 (0.91-1.10)	1.04 (0.94-1.15)
15-24	235 079	545	1.00 (0.92-1.10)	1.06 (0.96-1.17)
≥25	143 503	343	1.11 (0.99-1.24)	1.14 (1.02-1.29)
P for trend			.18	.02
Past amount of smoking, cigarettes/d				
Never smoker	1 341 442	3788	1 [Reference]	1 [Reference]
1-14	519 339	1659	1.05 (0.99-1.11)	1.02 (0.97-1.09)
15-24	355 624	1212	1.14 (1.06-1.21)	1.11 (1.04-1.18)
≥25	172 765	583	1.12 (1.03-1.22)	1.08 (0.99-1.18)
P for trend			<.001	.003
Age one started smoking, y				
Never smoker	1 341 442	3788	1 [Reference]	1 [Reference]
≥20	721 330	2199	1.04 (0.98-1.09)	1.04 (0.99-1.11)
18-19	633 381	1826	1.06 (1.00-1.12)	1.08 (1.01-1.14)
≤17	341 835	968	1.07 (0.99-1.15)	1.07 (0.99-1.15)
P for trend			.02	.01
Duration of smoking, y				
Never smoker	1 341 442	3788	1 [Reference]	1 [Reference]
<20	617 370	1580	1.08 (1.01-1.14)	1.04 (0.98-1.11)
20-39	753 013	2092	1.06 (1.00-1.12)	1.07 (1.00-1.14)
≥40	253 225	902	1.08 (0.99-1.17)	1.15 (1.04-1.27)
P for trend			.02	.01
Years since quitting				
Never smoker	1 341 442	3788	1 [Reference]	1 [Reference]
≥20	427 489	1613	1.09 (1.03-1.16)	1.05 (0.99-1.12)
10-19	309 881	935	1.07 (1.00-1.15)	1.03 (0.96-1.11)
<10	332 579	995	1.11 (1.04-1.19)	1.09 (1.02-1.17)
Current smoker	586 952	1422	1.02 (0.96-1.09)	1.05 (0.99-1.12)
P for trend			.14	.08

Abbreviation: NHS, Nurses' Health Study.

[a] Adjusted for age, family history of breast cancer, age at menarche, height, body mass index at age 18 years, oral contraceptive use, history of benign breast disease, leisure-time physical activity, alcohol consumption, passive smoking at home and at work, age at first birth, and parity. Current smoking status was also adjusted for in the analysis of the age one started smoking, duration of smoking, and years since quitting.

other risk factors of BC (hazard ratio [HR] [95% confidence interval (CI)],1.04 [1.01-1.07]). Because the association between smoking and BC became stronger after adjusting for menopause-related factors, it is likely that this association was partially mediated by an early onset of menopause induced by smoking.[18] Therefore, we decided not to adjust for menopause-related factors in the primary analyses of other smoking measures to estimate the overall effect of smoking, which includes a potentially reduced risk conferred by inducing early onset of menopause.[23,24]

The covariate-adjusted HR was slightly elevated among women who smoked 25 or more cigarettes a day currently or in the past, who started to smoke at or before age 17 years, who smoked for 20 to 39 years or for 40 years or longer, or who had quit smoking within the past 10 years (**Table 3**). Measures of smoking, such as duration and age started (r=0.78), duration and current quantity (r=0.91) and past quantity (r=0.87), age started and current quantity (r=0.96) and past quantity (r=0.89), were highly correlated. An indicator for heavy smoking that integrates all 3 measures of smoking was created. Heavy smokers who started smoking before age 18 years and who smoked for more than 35 years with more than 25 cigarettes a day had an HR (95% CI) of 1.25 (1.06-1.46) compared with never smokers in covariate-adjusted analysis.

When smoking during various reproductive life periods was assessed, every increase of 20 pack-years of smoking from menarche to menopause was associated with a slightly increased incidence of BC (HR [95% CI], 1.11 [1.07-1.15]) in covariate-adjusted analysis (**Table 4**). The association was stronger for smoking before the first birth (HR [95% CI], 1.18 [1.10-1.27]) than after the first birth but before menopause (1.04 [0.99-1.10]) (*P* for heterogeneity = .007). Every increase of 20 pack-years of smoking after menopause was associated with a marginally decreased incidence of BC (HR [95% CI], 0.93 [0.85-1.02]). The association between pack-years of smoking and BC incidence in covariate-adjusted analysis was significantly different across the 3 reproductive periods (eg, from menarche to first birth, from first birth to menopause, and after menopause) (*P* for heterogeneity < .001) and by menopausal status alone (*P* for heterogeneity < .001). When postmenopausal person-years were stratified by the use of HT, smoking after menopause was not associated with the incidence of BC in per-

Table 4. Pack-years of Smoking Relevant to Menarche, Age at First Birth, and Menopause in Relation to Incidence of Breast Cancer Among 111 140 Participants in the NHS

Exposure	Person-years	No. of Cases	Hazard Ratio (95% Confidence Interval)		
			Age-Adjusted	Covariate-Adjusted I[a]	Covariate-Adjusted II[b]
Smoking from menarche to before menopause, pack-years					
0	1 377 249	3871	1 [Reference]	1 [Reference]	1 [Reference]
1-10	568 388	1518	1.01 (0.95-1.07)	1.04 (0.98-1.11)	1.01 (0.95-1.08)
11-20	490 136	1412	1.08 (1.01-1.14)	1.16 (1.08-1.24)	1.14 (1.06-1.22)
21-30	365 237	1123	1.05 (0.99-1.13)	1.16 (1.08-1.26)	1.15 (1.07-1.24)
≥31	251 164	891	1.15 (1.07-1.24)	1.28 (1.18-1.39)	1.27 (1.16-1.38)
P for trend			<.001	<.001	<.001
Every increase of 20 pack-years			1.06 (1.03-1.09)	1.11 (1.07-1.15)	1.11 (1.07-1.15)
Smoking from menarche to before first birth, pack-years					
0	1 493 714	4174	1 [Reference]	1 [Reference]	1 [Reference]
1-5	1 014 089	2889	1.04 (0.99-1.09)	1.12 (1.05-1.21)	1.11 (1.04-1.20)
6-10	340 148	1060	1.14 (1.07-1.22)	1.22 (1.12-1.33)	1.19 (1.09-1.30)
11-15	103 217	335	1.18 (1.06-1.32)	1.25 (1.11-1.41)	1.21 (1.07-1.36)
≥16	101 006	357	1.22 (1.10-1.36)	1.30 (1.16-1.46)	1.25 (1.11-1.40)
P for trend			<.001	<.001	<.001
Every increase of 20 pack-years			1.20 (1.12-1.28)	1.22 (1.14-1.31)	1.18 (1.10-1.27)
Smoking after first birth to before menopause, pack-years					
0	1 641 615	4678	1 [Reference]	1 [Reference]	1 [Reference]
1-10	580 834	1563	1.02 (0.96-1.08)	0.95 (0.88-1.04)	0.94 (0.86-1.02)
11-20	448 257	1292	1.04 (0.98-1.11)	0.99 (0.90-1.09)	0.99 (0.90-1.09)
21-30	258 604	848	1.08 (1.00-1.16)	1.04 (0.94-1.16)	1.04 (0.94-1.16)
≥31	122 864	434	1.12 (1.01-1.23)	1.07 (0.94-1.21)	1.05 (0.92-1.19)
P for trend			.005	.05	.05
Every increase of 20 pack-years			1.05 (1.01-1.09)	1.04 (0.98-1.10)	1.04 (0.99-1.10)
Smoking after menopause, pack-years					
0	1 375 058	4946	1 [Reference]	1 [Reference]	1 [Reference]
1-5	256 793	839	1.00 (0.93-1.08)	0.91 (0.84-0.99)	0.94 (0.86-1.02)
6-10	142 069	465	0.94 (0.85-1.03)	0.83 (0.75-0.92)	0.89 (0.80-0.99)
11-15	87 360	313	0.96 (0.85-1.07)	0.83 (0.73-0.94)	0.90 (0.79-1.02)
≥16	111 990	424	0.94 (0.85-1.03)	0.81 (0.73-0.91)	0.88 (0.79-0.99)
P for trend			.08	<.001	.02
Every increase of 20 pack-years			0.96 (0.89-1.03)	0.87 (0.79-0.95)	0.93 (0.85-1.02)
Smoking after menopause without HT, pack-years					
0	965 772	3211	1 [Reference]	1 [Reference]	1 [Reference]
1-5	204 160	610	1.00 (0.92-1.10)	0.90 (0.81-1.00)	0.93 (0.84-1.03)
6-10	103 311	310	0.93 (0.82-1.04)	0.81 (0.71-0.93)	0.87 (0.76-0.99)
11-15	61 052	197	0.93 (0.81-1.08)	0.80 (0.68-0.94)	0.88 (0.75-1.03)
≥16	70 714	252	0.95 (0.83-1.08)	0.82 (0.71-0.95)	0.90 (0.78-1.05)
P for trend			.16	<.001	.08
Every increase of 20 pack-years			0.95 (0.86-1.05)	0.86 (0.77-0.97)	0.93 (0.83-1.05)
Smoking after menopause with HT, pack-years					
0	401 980	1778	1 [Reference]	1 [Reference]	1 [Reference]
1-5	77 295	320	1.03 (0.91-1.16)	1.02 (0.87-1.18)	1.02 (0.87-1.19)
6-10	25 937	99	0.91 (0.74-1.12)	0.87 (0.69-1.09)	0.89 (0.70-1.12)
≥11	21 963	118	1.18 (0.98-1.43)	1.14 (0.91-1.41)	1.10 (0.88-1.37)
P for trend			.29	.61	.74
Every increase of 20 pack-years			1.18 (0.97-1.42)	1.15 (0.93-1.43)	1.11 (0.89-1.39)

Abbreviations: HT, hormone therapy; NHS, Nurses' Health Study.

[a] In the assessment of smoking during a specific life period, smoking during the other life periods was adjusted for.

[b] Additionally adjusted for family history of breast cancer, history of benign breast disease, age at menarche, age at first birth, parity, oral contraceptive use, height, current body mass index, body mass index at age 18 years, physical activity, alcohol consumption, passive smoking status at home, and passive smoking status at work. Parity and age at first birth were not adjusted for in the analysis of smoking from menarche to before first birth or in the analysis of smoking after first birth to before menopause. Postmenopausal HT use was adjusted for in the analysis of smoking after menopause.

son-years with or without HT, and the test for heterogeneity by HT was not significant (*P*=.17). When we restricted the analysis to postmenopausal women without any HT at the person-level, the results were similar to those restricted to person-years without HT.

The association of BC incidence with number of cigarettes a day when women started smoking (*P* for interaction=.68) or stopped smoking (*P* for interaction=.15) did not differ significantly among women who increased or decreased their BMI within 2 years after stopping or starting smoking or women whose BMI remained unchanged. Analyses separately assessing premenopausal BC (*P* for interaction=.07 and .12 for starting and stopping smoking, respectively) and postmenopausal BC (*P* for interaction=.11 and .58 for starting and stopping smoking, respectively) generated similar results.

When BC was classified by ER and PR status, smoking (every increase of 20 pack-years) after menarche appeared to be more consistently associated with ER-positive BC (HR [95% CI], 1.05 [1.01-1.08]) than with ER-negative BC (1.02 [0.95-1.09]) and with PR-positive BC (1.06 [1.02-1.10]) than with PR-negative BC (1.01 [0.95-1.06]) in covariate-adjusted analysis, although test results for heterogeneity were not significant (P=.15 for ER status and P=.29 for PR status). The test results for heterogeneity by ER status were statistically significant for pack-years of postmenopausal smoking (P for heterogeneity=.002) and postmenopausal smoking without HT (P for heterogeneity=.006) but not for postmenopausal smoking with HT (P for heterogeneity=.59). However, when the magnitude was assessed, the negative associations of every increase of 20 pack-years of postmenopausal smoking and postmenopausal smoking without HT with the incidence of BC were not substantially different for ER-positive BC (HR [95% CI], 0.92 [0.82-1.03] and 0.97 [0.83-1.12], respectively) and ER-negative BC (0.85 [0.66-1.10] and 0.79 [0.56-1.13], respectively). Postmenopausal smoking in relation to the incidence of BC was not significantly different by PR status. The association between premenopausal smoking and the incidence of BC did not differ significantly by ER or PR status (data not shown).

When the analysis of active smoking was stratified by passive smoking status, every increase of 20 pack-years of smoking after menarche appeared to be more consistently associated with the incidence of BC among women who were regularly exposed to passive smoking (HR [95% CI], 1.08 [1.03-1.12]) than among those who were never or occasionally exposed (1.01 [0.97-1.06]) in covariate-adjusted analysis, but the test results for heterogeneity were not significant (P=.08).

When analyses were stratified by menopausal status when BC was diagnosed, active smoking was not differentially associated with premenopausal BC relative to postmenopausal BC for various assessed smoking measures. For instance, when pack-years of premenopausal smoking in association with premenopausal BC and postmenopausal BC was assessed, no significant heterogeneity was found for premenopausal smoking overall (P=.81), smoking before first birth (P=.26), or smoking between first birth and menopause (P=.46).

Exposure to parental smoking when living with them, exposure to passive smoking at work or at home, the number of years living with someone who smokes, and the index of passive smoking were not related to the incidence of BC in covariate-adjusted analyses (**Table 5**).

COMMENT

In the present study, various measures of smoking, including ever smoking, current and past quantity, age at which one started smoking, duration, years since quitting smoking, and pack-years of smoking after menarche were associated with a marginally higher incidence of BC. Smoking before menopause, especially before the first birth, was associated with a slightly increased incidence of BC.

The associations of BC risk with quantity of smoking,[25-38] duration of smoking[19,32,35-37,39] and age at which one started smoking[19,29,32,33,35-39] have been investigated in many previous studies. The results remain partly conflicting, but positive associations have been reported among heavy smokers, long-time smokers, and smokers who started at an early age. In most of the previous studies, these smoking measures were not mutually adjusted. In the present study, we created an index of active smoking that integrates quantity, age at which one started smoking, and duration of smoking. The results suggested that, although an elevated risk for light smokers and moderate smokers was not apparent, heavy smokers who started smoking early in life, smoked for a long duration, and smoked a high quantity were at the highest risk of BC, supporting an independent and additive effect from various smoking measures on breast carcinogenesis.

Results from the present study suggest that the initiation of smoking before menopause and particularly before the first birth was most strongly associated with an increased risk of BC. Early age at the first birth has been found to convey a long-term protection against BC, possibly because of the terminal differentiation of breast epithelium late in the last trimester of the pregnancy.[40] Therefore, the experience of a full-term pregnancy may be a better indicator than age of the maturity and decreased susceptibility of breast cells to carcinogens. All previous studies that have separately evaluated smoking before and after the first birth have found a similar pattern, suggesting that smoking before the first birth may be more important to breast carcinogenesis than smoking after the first birth.[19,37-39,41,42]

Smoking before menopause was positively associated with BC risk, and there were hints from our results that smoking after menopause might be associated with a slightly decreased BC risk. This difference suggests an antiestrogenic effect of smoking[15] among postmenopausal women that may further reduce their already low endogenous estrogen levels. Conversely, among premenopausal women, any antiestrogenic effect of smoking may not be strong enough to significantly reduce endogenous estrogen levels, leaving the dominant carcinogenic effect of smoking.[3,5-14] A similar dual effect of smoking before and after menopause was reported by Band et al[43] but not in other studies.[37,38]

Extensive exposure to passive smoking has been suggested to induce BC development because *N*-nitrosamines and other carcinogens found in tobacco smoke appear to be more concentrated in passive smoke than in mainstream smoke.[44] In 8[45-52] of 9 case-control studies,[45-53] a positive association between passive smoking and risk of BC was found, and in 7 studies this association was statistically significant.[45-50,52] In contrast to the strong evidence from case-control studies, only 1[54] of 6 cohort studies[19,37,38,54-56] identified a significantly increased risk of BC among women who were exposed to 51 hours/d–years or more of lifetime passive smoking relative to those never exposed. In the present study, incidence of BC was not related to frequency or duration of

Table 5. Passive Smoking in Relation to Incidence of Breast Cancer Among Nonsmokers

Passive Smoking Status	Person-years	No. of Cases	Hazard Ratio (95% Confidence Interval)	
			Age-Adjusted	Covariate-Adjusted[a]
Exposure to parental smoking when living with them				
Neither smoked	342 457	1156	1 [Reference]	1 [Reference]
Mother only	33 107	81	0.80 (0.63-1.00)	0.83 (0.66-1.05)
Father only	378 859	1313	1.02 (0.95-1.11)	1.01 (0.93-1.10)
Both parents	120 522	333	0.91 (0.81-1.03)	0.90 (0.79-1.03)
Exposure at work				
Never	186 896	637	1 [Reference]	1 [Reference]
Occasionally	362 062	1210	1.00 (0.90-1.10)	0.99 (0.89-1.09)
Regularly	210 505	621	0.89 (0.79-0.99)	0.87 (0.78-0.98)
Exposure at home				
Never	424 368	1374	1 [Reference]	1 [Reference]
Occasionally	207 918	721	1.05 (0.95-1.15)	1.06 (0.97-1.17)
Regularly	126 169	402	0.98 (0.88-1.10)	1.02 (0.90-1.14)
Years living with someone who smokes				
Never or <1	384 292	1243	1 [Reference]	1 [Reference]
1-4	83 662	290	1.09 (0.96-1.24)	1.09 (0.96-1.24)
5-9	65 670	215	0.96 (0.83-1.11)	0.98 (0.84-1.13)
10-19	135 986	423	0.96 (0.86-1.07)	0.96 (0.86-1.08)
20-29	121 069	404	0.95 (0.85-1.07)	0.96 (0.85-1.08)
30-39	66 210	249	0.93 (0.80-1.07)	0.97 (0.84-1.13)
≥40	13 605	50	0.96 (0.72-1.28)	0.99 (0.74-1.32)
P for trend			.17	.24
Index of passive smoking				
Neither at work nor at home	139 088	449	1 [Reference]	1 [Reference]
Occasional exposure at home or work of <20 y	279 151	921	1.09 (0.97-1.22)	1.09 (0.97-1.22)
Occasional exposure at home or work of ≥20 y	87 259	296	0.97 (0.83-1.12)	1.00 (0.86-1.16)
Regular exposure at home or work of <20 y	89 980	263	0.99 (0.85-1.16)	0.99 (0.85-1.16)
Regular exposure at home or work of ≥20 y	54 846	180	0.96 (0.81-1.14)	0.97 (0.81-1.16)

[a] Adjusted for age, family history of breast cancer, history of benign breast disease, body mass index, body mass index at age 18 years, height, alcohol consumption, age at menarche, parity, age at first birth, physical activity, oral contraceptive use, menopausal status, postmenopausal hormone use, and age at menopause. Passive smoking at home and passive smoking at work were adjusted for each other. Exposure to parental smoking in childhood was adjusted for in the analysis on passive smoking in adulthood.

passive smoking in adulthood or to exposure to parental smoking in childhood. Our results combined with the evidence from previous prospective cohort studies collectively suggest that passive smoking may not play an important role in the etiology of BC. Nonetheless, we found that regular exposure to passive smoking may magnify the effect of active smoking. This effect was not explained by higher smoking intensity among smokers who were also regularly exposed to passive smoking because we found the same pattern of effect modification for all smoking measures, including duration, quantity, and age at which one started smoking. Such interaction has not been explored in previous studies, and further evidence is warranted to confirm our finding and to explore potential mechanisms.

A limitation of the present study is the limited quantitative and updated assessment of passive smoking, which introduces the potential for misclassification. Compared with active smoking, passive smoking is more difficult to assess because of its ubiquitous presence. Previous studies[19,37,38,45-56] on passive smoking have used various quantitative measures, such as quantity and duration of husband's smoking, pack-years of lifetime exposure, and hours per day–years, but none of these measures has been suggested to be superior. Any nondifferential misclassification of passive smoking in our study would bias the association toward the null.

To our knowledge, the present study is the largest so far on the association between smoking and BC risk. The substantial statistical power allows us to detect even a modest association. The prospective cohort design and updated information on quantity and status of active smoking prevented recall bias and minimized the chances for selection bias and nondifferential misclassification of smoking due to changes in behavior over time. The Nurses' Health Study provides information on a variety of covariates, including potential confounders, effect modifiers, and hormone receptor status of BC, and allows exploration of mechanistic associations.

Despite the extensive research on cigarette smoking in relation to BC risk, this association remains controversial. Results from the present study suggest that the potential effect of active smoking on BC risk is modest. The risk of BC may increase with younger age at smoking initiation and longer duration of smoking. Antiestrogenic effects of smoking, which may convey a reduced risk of BC, are suggested to be more dominant among postmenopausal women. Growing evidence suggests that carcinogen-metabolizing genes may modify the potential effect of smoking on risk of BC.[57] Future studies with large numbers of cases are needed to address this issue in a level of detail similar to that provided in this analysis.

Accepted for Publication: June 11, 2010.
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Financial Disclosure: None reported.
Funding/Support: The Nurses' Health Study is supported by grant CA87969 from the National Cancer Institute, National Institutes of Health.
Additional Contributions: Karen Corsano, BA, Brigham and Women's Hospital, provided technical assistance, and Marion McPhee, BEd, provided SAS programming advice.

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Images From Our Readers

Courtesy of: Albert B. Levin, MD, Cardiovascular Medicine, Lahey Clinic, Burlington, Massachusetts.

The major limitations of the present study are its observational nature and the lack of any objective measure of patients' adherence to prescribed drug regimens. Furthermore, owing to the limited number of patients, we could not fully adjust for potential confounders, such as the presence of the cardiovascular comorbidities for which the β-blockers had been prescribed, nor could we conduct separate analyses for β-blockers with different pharmacological properties. Despite these limitations, we believe that the results of this initial report are sufficient to support conducting larger pharmaco-epidemiological studies and randomized clinical trials to further investigate whether β-blockers protect against the progression of malignant melanoma.

Accepted for Publication: November 27, 2011.
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Author Contributions: Dr De Giorgi had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* De Giorgi and Geppetti. *Acquisition of data:* De Giorgi, Grazzini, Gandini, and Lotti. *Analysis and interpretation of data:* De Giorgi, Benemei, and Grazzini. *Drafting of the manuscript:* Benemei and Grazzini. *Critical revision of the manuscript for important intellectual content:* De Giorgi, Grazzini, Benemei, Lotti, Marchionni, and Geppetti. *Statistical analysis:* Grazzini and Gandini. *Study supervision:* De Giorgi, Lotti, Marchionni, and Geppetti.
Financial Disclosure: None reported.

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Correction

Errors in Table. In the Original Article titled "Cigarette Smoking and the Incidence of Breast Cancer" by Xue et al, published in the January 24, 2011, issue of the *Archives* (2011;171[2]:125-133), incorrect categories for age at start of smoking appeared in **Table 3**. The article was corrected online.