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Cigarette smoking and the incidence of Breast Cancer

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Abstract

Background—Tobacco smoke contains carcinogens which may increase the risk of breast cancer (BC). Conversely, cigarette smoking also has anti-estrogenic 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 79,010 women from 1982 to 2006 for passive smoking.

Results—During 3,005,863 person-years (PYs) of follow-up, 8,772 incident cases of invasive BC were reported. After adjustment for potential confounders, the hazard ratio (HR) of BC was 1.06% (95% CI 1.01% – 1.11%) for ever smokers relative to never smokers. BC incidence was associated with higher quantity of current (P for trend=0.02) and past smoking (P for trend=0.003), younger age of initiation (P for trend=0.01), longer duration (P for trend=0.01) and more PKY (PKY) of smoking (P for trend=0.005). While premenopausal smoking was associated with a slightly higher incidence of BC (HR=1.11, 95% CI 1.07 – 1.15 for increase of every 20-PKY) especially smoking before first birth (HR=1.18, 95% CI 1.10 – 1.27 for increase of every 20-PKY), the direction of the association between postmenopausal smoking and BC was reversed (HR=0.93, 95% CI 0.85 – 1.02 for increase of every 20-PKY). Passive smoking in childhood or adulthood was not associated with BC risk.

Conclusion—Results from this large prospective cohort study suggest that active smoking especially smoking before first birth may be associated with a modest increase in the risk of BC.

Introduction

Breast cancer (BC) is the most common female cancer worldwide (1). The annual incidence range from 11.8 per 100,000 in Eastern China to 86.3 per 100,000 in North America (2), suggesting the influence of environmental or life style factors in the etiology of BC. Tobacco smoking is one of the leading preventable risk factors of cancer in respiratory and non-respiratory sites (3,4). Tobacco smoke contains potential human breast carcinogens including polycyclic aromatic hydrocarbons (PAHs), aromatic amines and N-nitrosamines (3,5–7). Carcinogens in tobacco pass through the alveolar membrane and enter the blood

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stream (8), and are transported to mammary tissue through plasma lipoproteins (9,10). Indeed, metabolites of cigarette smoke have been detected in the breast fluid of nonlactating cigarette smokers obtained through standard nipple aspiration technique (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 anti-estrogenic effect (15) which may be associated with a lower risk of BC. The anti-estrogenic 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 replacement therapy (HRT) among smokers (16).

Numerous epidemiologic studies 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 (13). 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 is comprised of many facets, including active and passive smoking, as well as quantity, duration, cessation, and initiation of smoking, which are difficult to assess accurately. In case-control studies recall bias has to be considered.

We have previously reported a slightly elevated relative risk of BC among active but not passive smokers from the Nurses' Health Study (NHS) based on follow-up from 1982 to 1996 including 3140 BCs, especially when smoking was initiated at a young age (19). We here present an updated analysis including follow-up from 1976 to 2006 and adding 5632 incident cases, including assessment of potential effect of multiple measures of active and passive smoking and smoking during various reproductive periods.

Methods

The NHS is a large prospective cohort established in 1976. At baseline, 121,700 married female nurses aged 30 to 55 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 women who did not have prevalent invasive or in situ BC or other cancers and 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 women who did not have prevalent invasive or in situ BC or other cancers, never smoked and provided information on passive smoking in 1982. All included women were followed biennially from cohort entry (1976 for active smoking analysis and 1982 for passive smoking analysis) until the earliest of diagnosis of invasive or in situ BC, loss to follow-up, death or the end of study period in 2006. Women lost to follow-up in each cycle were not followed for that cycle but could reenter the analysis if they responded to a next questionnaire. For the analysis on passive smoking, the follow-up also ended when women started smoking, to eliminate the effect of active smoking. The follow-up rate calculated as eligible person-years (Pys) divided by maximum possible Pys assuming no loss to follow-up was 82.5% for active smoking analysis and 89.0% the passive smoking analysis. This study was approved by the Institutional Review Board of the Brigham and Women's Hospital in Boston, Massachusetts.

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 their age at which they started smoking, whether they ever quitted smoking for 6 or more months and at what age they quitted smoking. Questions related to passive smoking including parental smoking status when living with them, years living with a smoker in adulthood, as well as status and frequency of exposure to cigarette smoke at home and work were asked in 1982.

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

Ascertainment of BC

Participants were asked biennially whether they had been diagnosed with BC during the past two years and, if so, to report the date of diagnosis. Deaths were reported by next of kin or by the U.S. 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 current study, we included invasive BC confirmed by medical record or by the nurses themselves, since self-reports of BC have been found to be highly reliable. Medical record-adjudicated BC cases accounts for 88.0% and 87.7% of all included cases for the analysis on active and passive smoking, respectively.

Assessment of Other Covariates

NHS participants were asked about their reproductive factors, anthropometric characteristics, life style and diagnosis of other diseases biennially. Current body mass index (BMI) and BMI at age 18 were calculated as weight/height^2 (kg/m^2)using weight at the respective age and height in adulthood. Assessment of age, parity, current weight, alcohol consumption, physical activity, OC use, menopausal status, age at menopause, HRT use, history of benign breast disease, and family history of BC were updated during follow-up.

Statistical Analysis

A Cox proportional hazard 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 started smoking, duration of smoking, years since quitting smoking, and PKY 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 years with someone who smokes in defined categories. We also derived an index of passive smoking integrating both 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 performed based on the midpoint value of each category.

Potential confounding factors considered include age, family history of BC among first degree relatives, age at menarche, height, BMI at age 18, oral contraceptive (OC) use, history of benign breast disease, leisure time physical activity, alcohol consumption, a derived variable cross-stratifying age at first birth by parity, current body mass index (BMI), age at menopause, menopausal status, and HRT use. Updated history of mammogram screening and types of HRT (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 analysis of the quantitative smoking measures (quantity, age started, duration, and PKY).

Since smoking cessation is related to weight gain (22), which may increase the risk of BC for postmenopausal women (1), potential effect modification of number of cigarettes per day when started and stopped smoking by changes in body mass index (BMI) was assessed by stratified analyses and the significance of effect modification was evaluated. Potential heterogeneity in the association between smoking and BC across various reproductive periods was assessed using a fixed-effect meta-analysis of effect estimates derived from each period, weighted by the inverse variance. A polychotomous logistic regression (PLR) software (23) 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 8,772 incident cases of BC arose during 3,005,863 PYs of follow-up from 1976 to 2006. Relative to PYs with other smoking status, current smokers were more likely to be postmenopausal and had a lower current BMI; past smokers were more likely to have a family history of BC, a history of benign breast disease and ever used OC; and never smokers tended to consume less alcohol. A total of 2,890 incident cases of BC occurred during 876,996 PYs 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 have used OC.

Ever smokers had a marginally increased incidence of BC than never smokers and the increase in incidence seemed to be comparable for past smokers and current smokers (Table 2). Every 20-PKY of smoking after menarche was associated with a marginal increase of incidence of breast after adjusting for other risk factors of BC [HR (95% CI)= 1.04 (1.01 – 1.07)]. Since the association between smoking and BC became stronger after adjusting for menopause-related factors, it is likely that this association is partially mediated through 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 potential effect of smoking including a potential reduced risk by inducing early onset of menopause (20, 21).

The covariate-adjusted hazard ratio (HR) was slightly elevated among women who smoked ≥25 cigarettes per day currently or in the past, who started to smoke at age ≤17 years, who smoked for 20–39 years or ≥40 years, or who quitted 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 integrating all three measures of smoking was created. Heavy smokers who started smoking before 18 years of age and smoked for over 35 years with more than 25 cigarettes per day

had a HR of 1.25 (95% CI 1.06 – 1.46) compared to never smokers in covariate-adjusted analysis.

When smoking during various reproductive life periods was assessed, every 20-PKY 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 first birth [HR (95% CI)=1.18 (1.10 – 1.27)] than after first birth but before menopause [HR (95% CI)=1.04 (0.99 – 1.10)] (P for heterogeneity=0.007). Every 20-PKY 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 PKY of smoking and BC incidence in covariate-adjusted analysis was significantly different across the three reproductive periods (e.g., from menarche to first birth, from first birth to menopause, and after menopause) (P for heterogeneity=0.0002) and by menopausal status alone (P for heterogeneity = 0.0004). When postmenopausal PYs were stratified by the use of HRT, smoking after menopause was not associated with the incidence of BC in PYs with or without HRT, and the test for heterogeneity by HRT was not significant (P=0.17). When restricting the analysis to postmenopausal women without any HRT at person-level, results were similar to those restricted to PYs without HRT.

The association of BC incidence with number of cigarettes per day when started smoking (P for interaction=0.68) or stopped smoking (P for interaction=0.15) did not differ significantly among women who increased or decreased their BMI within two years after stopping or starting smoking or whose BMI remained unchanged. Analyses separately assessing premenopausal (P for interaction =0.07 and 0.12 for starting and stopping smoking, respectively) and postmenopausal breast cancer generated similar results (P for interaction=0.11 and 0.58 for starting and stopping smoking, respectively).

When BC was classified by ER and PR status, smoking (every 20-PKY) after menarche appeared to be more consistently associated with ER+ [HR (95% CI)= 1.05 (1.01 – 1.08)] than ER- BC [HR (95% CI)= 1.02 (0.95 – 1.09)], and with PR+ [HR (95% CI)= 1.06 (1.02 – 1.10)] than PR- BC [HR (95% CI)= 1.01 (0.95 – 1.06)] in covariate-adjusted analysis, though tests for heterogeneity was not significant (P =0.15 for ER status, P =0.29 for PR status). The test for heterogeneity by ER status was statistically significant for PKY of postmenopausal smoking (P for heterogeneity=0.002) and postmenopausal smoking without HRT (P for heterogeneity=0.006), but not postmenopausal smoking with HRT (P for heterogeneity=0.59). However, when the magnitude was assessed, the negative association of postmenopausal and postmenopausal smoking (every 20-PKY) without HRT with the incidence of BC was not substantially different for ER positive BC [HR (95% CI)= 0.92 (0.82 – 1.03) and 0.97 (0.83 – 1.12), respectively] than for ER negative BC [HR (95% CI)= 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.

When the analysis of active smoking was stratified by passive smoking status, every 20-PKY after menarche appears 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 those who were never or occasionally exposed [HR (95% CI)= 1.01 (0.97 – 1.06)] in covariate-adjusted analysis, but the test for heterogeneity was not significant (P=0.08).

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 PKY of

premenopausal smoking in association with premenopausal BC and postmenopausal BC was assessed, no significant heterogeneity was found for premenopausal smoking overall (P=0.81), smoking before first birth (P=0.26) or smoking between first birth and menopause (P=0.46).

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

Discussion

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

The associations of BC risk with quantity of smoking (24–37), duration of smoking (19,31,34–36,38) and age started smoking (19,28,31,32,34–38) 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 integrating quantity, age started and duration of smoking. The results suggested that though an elevated risk for light smoker and moderate smoker was not apparent, heavy smokers who started smoking early in life, smoked for a long duration and with a high quantity were at the highest risk of BC, supporting independent and additive effect from various smoking measures on breast carcinogenesis.

Results from the current study suggest that the initiation of smoking before menopause and particularly before first full-term pregnancy was most strongly associated with an increased risk of BC. Early age at first full-term pregnancy 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 (39). Therefore, the experience of a full-term pregnancy may be a better indicator of the maturity and decreased susceptibility of breast cells to carcinogens than age. All previous studies that have separately evaluated smoking before and after the first full-term pregnancy have found a similar pattern, suggesting smoking before the first full-term pregnancy may be more important than smoking after the first pregnancy in breast carcinogenesis (19,36–38,40,41).

Smoking before menopause was positively associated with BC risk, while there were hints from our results that smoking after menopause might be associated with a slightly decreased BC risk. This difference suggests an anti-estrogenic effect of smoking (15) among postmenopausal women which may reduce their already low endogenous estrogen levels further. Conversely, among premenopausal women any anti-estrogenic 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 (42), but not in other studies (36, 37).

Extensive exposure to passive smoking has been suggested to induce BC development since nitrosamines and other carcinogens found in tobacco smoke appear to be more concentrated in passive smoke than in mainstream smoke (43). In eight (44–48, 50–52) of nine case-control studies (44–52), a positive association between passive smoking and risk of BC was found, and in seven studies this association was statistically significant (44–48, 50, 52). In contrast to the strong evidence from case-control studies, only one (53) of six cohort studies

(19,36,37,53–55) identified a significantly increased risk of BC among women who were expose to ≥51 hours/day-years lifetime passive smoking relative to those never exposed. In the current study, incidence of BC was not related to frequency or duration of 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 and it was not explained by higher smoking intensity among smokers who were also regularly exposed to passive smoking since we found the same pattern of effect modification for all smoking measures, including duration, quantity and age 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 current study is the limited quantitative and updated assessment of passive smoking, introducing the potential for misclassification. Compared to active smoking, passive smoking is more difficult to assess due to its ubiquitous presence. Previous studies on passive smoking have used various quantitative measures, such as quantity and duration of husband's smoking, PKY of life time exposure, hours/day-years, but none of these measures have been suggested to be superior. Any non-differential misclassification of passive smoking in our study would bias the association towards the null.

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 non-differential misclassification of smoking due to changes of 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, allow exploration of mechanistic associations.

Despite the extensive research on cigarette smoking in relation to BC risk, this association remains controversial. Results from the current study suggest the potential effect of active smoking on BC risk is modest. The risk of BC may increase with younger age of initiation and longer duration of smoking. Anti-estrogenic effects of smoking, which may convey a reduced risk of BC, are suggested to be more dominant among postmenopausal women. There is growing evidence suggesting carcinogen metabolizing genes may modify the potential effect of smoking on risk of BC (56). Future studies with large numbers of cases are needed to address this issue in similar detail to that provided in this analysis.

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Table 1

Age-standardized distribution of selected personal characteristics of person-years of follow-up according to active and passive smoking status.

Personal Characteristics	Active Smoking			Passive Smoking		
	Never	Past	Current	Never	Occasionally	Regularly
Age (years) (mean)	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:						
Number of children (mean)	3.2	3.1	3.2	3.1	3.2	3.2
Age at first birth (years) (mean)	24.9	24.8	24.7	25.2	24.8	24.6
Body mass index (mean) (kg/m^2)	25.8	25.9	24.4	25.5	26.0	26.8
Body mass index at 18 (mean) (kg/m^2)	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 OC (%)	46.2	51.9	46.6	46.1	46.9	48.5
Alcohol consumption (grams/day) (mean)	3.6	6.8	8.6	3.3	3.7	3.4

*At baseline of 1976, a total of 111,140 participants of NHS were included in the analysis of active smoking. At baseline of 1982, a total of 36,017 participants of NHS were included in the analysis of passive smoking.

Table 2

Smoking status and pack-years of smoking in relation to the incidence of breast cancer among 111,140 participants in the NHS with follow-up from 1976 to 2006.

Smoking status	Person-years	Cases	Age-adjusted HR(95% CI)	Covariate-adjusted I HR(95% CI)*	Covariate-adjusted II HR(95% CI)†
Smoking Status					
Never	1341442	3788	1.0	1.0	1.0
Ever:	1664421	4984	1.07 (1.03 – 1.12)	1.06 (1.01 – 1.10)	1.07 (1.02 – 1.12)
Current	586952	1422	1.02 (0.96 – 1.09)	1.05 (0.98 – 1.12)	1.09 (1.02 – 1.17)
Past	1077469	3562	1.09 (1.04 – 1.14)	1.06 (1.01 – 1.11)	1.06 (1.01 – 1.11)
Total smoking after menarche					
0	1341442	3788	1.0	1.0	1.0
1–10 pack-years	528586	1419	1.03 (0.97 – 1.09)	1.00 (0.94 – 1.07)	1.00 (0.94 – 1.07)
11–20 pack-years	418217	1155	1.08 (1.02 – 1.16)	1.07 (1.00 – 1.14)	1.08 (1.01 – 1.16)
21–30 pack-years	330255	949	1.03 (0.96 – 1.10)	1.04 (0.97 – 1.12)	1.07 (1.00 – 1.15)
31–40 pack-years	205490	713	1.10 (1.02 – 1.19)	1.12 (1.03 – 1.21)	1.16 (1.07 – 1.26)
41–50 pack-years	108847	365	0.98 (0.88 – 1.09)	1.01 (0.90 – 1.12)	1.05 (0.94 – 1.18)
≥51 pack-years	90966	365	1.11 (1.00 – 1.24)	1.14 (1.02 – 1.28)	1.19 (1.07 – 1.33)
P for trend			0.04	0.005	<0.0001
Ever 20 pack-years			1.03 (1.01 – 1.06)	1.04 (1.01 – 1.07)	1.06 (1.03 – 1.09)

*Covariate-adjusted I was adjusted for age (continuous), family history of breast cancer (yes, no), age at menarche (≤11, 12, 13, 14, ≥15 years), height (continuous), BMI at age 18 (continuous), OC use (never, ever for <1 year, ever for 1–4 years, ever for 5–10 years, ever for >10 years), history of benign breast disease (yes, no), leisure time physical activity (<1, 1–<2, 2–<4, 4–<7, ≥7 hours/week), alcohol consumption (0, 0.1–4.9, 5–14.9, ≥15 grams/day), passive smoking at home and at work (never, occasional, regular), age at first birth (nulliparous, ≤24 years, 25–29 years, 30–34 years, ≥35 years), parity (0, 1, 2, 3, ≥4), and current BMI (continuous).

†Covariate-adjusted II was additionally adjusted for age at menopause (continuous), menopausal status (premenopause, postmenopause, dubious), and postmenopausal hormone use (never, past for <5 years, past for ≥5 years, current for <5 years, current for ≥5 years).

Table 3

Age started smoking, duration of smoking, years since quitting and pack-years of smoking in relation to the incidence of breast cancer among 111,140 participants of NHS with follow-up from 1976 to 2006.

Current amount of smoking	Person-years	Cases	Age-adjusted HR(95% CI)	Covariate-adjusted HR(95% CI)*
Never	1341442	3788	1.0	1.0
1–14 cigs/day	189721	484	1.00 (0.91 – 1.10)	1.04 (0.94 – 1.15)
15–24 cigs/day	235079	545	1.00 (0.92 – 1.10)	1.06 (0.96 – 1.17)
≥25 cigs/day	143503	343	1.11 (0.99 – 1.24)	1.14 (1.02 – 1.29)
P for trend			0.18	0.02
Past amount of smoking				
Never	1341442	3788	1.0	1.0
1–14 cigs/day	519339	1659	1.05 (0.99 – 1.11)	1.02 (0.97 – 1.09)
15–24 cigs/day	355624	1212	1.14 (1.06 – 1.21)	1.11 (1.04 – 1.18)
≥25 cigs/day	172765	583	1.12 (1.03 – 1.22)	1.08 (0.99 – 1.18)
P for trend			<0.0001	0.003
Age at which started smoking				
Never smoker	1341442	3788	1.0	1.0
≥20 years	341835	968	1.07 (0.99 – 1.15)	1.07 (0.99 – 1.15)
18–19 years	633381	1826	1.06 (1.00 – 1.12)	1.08 (1.01 – 1.14)
≤17 years	721330	2199	1.04 (0.98 – 1.09)	1.04 (0.99 – 1.11)
P for trend			0.02	0.01
Duration of smoking:				
Never smoked	1341442	3788	1.0	1.0
<20 years	617370	1580	1.08 (1.01 – 1.14)	1.04 (0.98 – 1.11)
20–39 years	753013	2092	1.06 (1.00 – 1.12)	1.07 (1.00 – 1.14)
≥40 years	253225	902	1.08 (0.99 – 1.17)	1.15 (1.04 – 1.27)
P for trend			0.02	0.01
Years since quitting:				
Never smoker	1341442	3788	1.0	1.0
20+ years	427489	1613	1.09 (1.03 – 1.16)	1.05 (0.99 – 1.12)

Current amount of smoking	Person-years	Cases	Age-adjusted HR(95% CI)	Covariate-adjusted HR(95% CI)*
10–19 years	309881	935	1.07 (1.00 – 1.15)	1.03 (0.96 – 1.11)
<10 years	332579	995	1.11 (1.04 – 1.19)	1.09 (1.02 – 1.17)
Current smoker	586952	1422	1.02 (0.96 – 1.09)	1.05 (0.99 – 1.12)
P for trend			0.14	0.08

*Adjusted for age(continuous), family history of breast cancer (yes, no), age at menarche (≤11, 12, 13, 14, ≥15 years), height (continuous), BMI at age 18 (continuous), OC use (never, ever for <1 year, ever for 1–4 years, ever for 5–10 years, ever for >10 years), history of benign breast disease (yes, no), leisure time physical activity (<1, 1–<2, 2–<4, 4–<7, ≥7 hours/week), alcohol consumption (0, 0.1–4.9, 5–14.9, ≥15 grams/day), passive smoking at home and at work (never, occasional, regular), age at first birth (nulliparous, ≤24 years, 25–29 years, 30–34 years, ≥35 years), parity (0, 1, 2, 3, ≥4), and current BMI (continuous). Current smoking status was also adjusted for in the analysis of age started smoking, duration of smoking, and years since quitting.

Table 4

Pack-years of smoking relevant to menarche, age at first birth and menopause in relation to the incidence of breast cancer among 111,140 participants of NHS

Exposure	Person-years	Cases	Age-adjusted HR(95% CI)	Covariate-adjusted I HR(95% CI)*	Covariate-adjusted II HR(95% CI)†
Smoking from menarche to before menopause					
0	1377249	3871	1	1	1
1–10 pack-years	568388	1518	1.01 (0.95 – 1.07)	1.04 (0.98 – 1.11)	1.01 (0.95 – 1.08)
11–20 pack-years	490136	1412	1.08 (1.01 – 1.14)	1.16 (1.08 – 1.24)	1.14 (1.06 – 1.22)
21–30 pack-years	365237	1123	1.05 (0.99 – 1.13)	1.16 (1.08 – 1.26)	1.15 (1.07 – 1.24)
≥31 pack-years	251164	891	1.15 (1.07 – 1.24)	1.28 (1.18 – 1.39)	1.27 (1.16 – 1.38)
P for trend			0.0001	<0.0001	<0.0001
Every 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					
0	1493714	4174	1	1	1
1–5 pack-years	1014089	2889	1.04 (0.99 – 1.09)	1.12 (1.05 – 1.21)	1.11 (1.04 – 1.20)
6–10 pack-years	340148	1060	1.14 (1.07 – 1.22)	1.22 (1.12 – 1.33)	1.19 (1.09 – 1.30)
11–15 pack-years	103217	335	1.18 (1.06 – 1.32)	1.25 (1.11 – 1.41)	1.21 (1.07 – 1.36)
≥16 pack-years	101006	357	1.22 (1.10 – 1.36)	1.30 (1.16 – 1.46)	1.25 (1.11 – 1.40)
P for trend			<0.0001	<0.0001	<0.0001
Every 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					
0	1641615	4678	1	1	1
1–10 pack-years	580834	1563	1.02 (0.96 – 1.08)	0.95 (0.88 – 1.04)	0.94 (0.86 – 1.02)
11–20 pack-years	448257	1292	1.04 (0.98 – 1.11)	0.99 (0.90 – 1.09)	0.99 (0.90 – 1.09)
21–30 pack-years	258604	848	1.08 (1.00 – 1.16)	1.04 (0.94 – 1.16)	1.04 (0.94 – 1.16)
≥31 pack-years	122864	434	1.12 (1.01 – 1.23)	1.07 (0.94 – 1.21)	1.05 (0.92 – 1.19)
P for trend			0.005	0.05	0.05
Every 20 pack-years			1.05 (1.01 – 1.09)	1.04 (0.98 – 1.10)	1.04 (0.99 – 1.10)
Smoking after menopause					
0	1375058	4946	1	1	1

Exposure	Person-years	Cases	Age-adjusted HR(95% CI)	Covariate-adjusted I HR(95% CI)*	Covariate-adjusted II HR(95% CI)†
1–5 pack-years	256793	839	1.00 (0.93 – 1.08)	0.91 (0.84 – 0.99)	0.94 (0.86 – 1.02)
6–10 pack-years	142069	465	0.94 (0.85 – 1.03)	0.83 (0.75 – 0.92)	0.89 (0.80 – 0.99)
11–15 pack-years	87360	313	0.96 (0.85 – 1.07)	0.83 (0.73 – 0.94)	0.90 (0.79 – 1.02)
≥16 pack-years	111990	424	0.94 (0.85 – 1.03)	0.81 (0.73 – 0.91)	0.88 (0.79 – 0.99)
P for trend			0.08	<0.0001	0.02
Every 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 hormone replacement therapy					
0	965772	3211	1	1	1
1–5 pack-years	204160	610	1.00 (0.92 – 1.10)	0.90 (0.81 – 1.00)	0.93 (0.84 – 1.03)
6–10 pack-years	103311	310	0.93 (0.82 – 1.04)	0.81 (0.71 – 0.93)	0.87 (0.76 – 0.99)
11–15 pack-years	61052	197	0.93 (0.81 – 1.08)	0.80 (0.68 – 0.94)	0.88 (0.75 – 1.03)
≥16 pack-years	70714	252	0.95 (0.83 – 1.08)	0.82 (0.71 – 0.95)	0.90 (0.78 – 1.05)
P for trend			0.16	<0.001	0.08
Every 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 hormone replacement therapy					
0	401980	1778	1	1	1
1–5 pack-years	77295	320	1.03 (0.91 – 1.16)	1.02 (0.87 – 1.18)	1.02 (0.87 – 1.19)
6–10 pack-years	25937	99	0.91 (0.74 – 1.12)	0.87 (0.69 – 1.09)	0.89 (0.70 – 1.12)
≥11 pack-years	21963	118	1.18 (0.98 – 1.43)	1.14 (0.91 – 1.41)	1.10 (0.88 – 1.37)
P for trend			0.29	0.61	0.74
Every 20 pack-years			1.18 (0.97 – 1.42)	1.15 (0.93 – 1.43)	1.11 (0.89 – 1.39)

*In the assessment of smoking during specific life period, smoking during the other life periods were adjusted for.

†Additionally adjusted for family history of breast cancer (yes, no), history of benign breast disease (yes, no), age at menarche (≤11, 12, 13, 14, ≥15 years), age at first birth (nulliparous, ≤24 years, 25–29 years, 30–34 years, ≥35 years), parity (0, 1, 2, 3, ≥4), OC use (never, ever for <1 year, ever for 1–4 years, ever for 5–10 years, ever for >10 years), height (continuous), current BMI (continuous), BMI at age 18 (continuous), physical activity (<1, 1–<2, 2–<4, 4–<7, ≥7 hours/week), alcohol consumption (0, 0.1–4.9, 5–14.9, ≥15 grams/day), passive smoking status at home and passive smoking status at work (never, occasional, regular). Parity and age at first birth were not adjusted for in the analysis of smoking from menarche to before first birth and analysis of smoking after first birth to before menopause. Postmenopausal hormone use (never, past for <5 years, past for ≥5 years, current for <5 years, current for ≥5 years) was adjusted in the analysis of smoking after menopause.

Table 5

Passive smoking in relation to the incidence of breast cancer among nonsmokers

Passive smoking status	Person-years	Cases	Age-adjusted HR(95% CI)	Covariate-adjusted HR(95% CI)*
Exposure to parental smoking when living with them				
Neither smoked	342457	1156	1.0	1.0
Mother only	33107	81	0.80 (0.63, 1.00)	0.83 (0.66, 1.05)
Father only	378859	1313	1.02 (0.95, 1.11)	1.01 (0.93, 1.10)
Both parents	120522	333	0.91 (0.81, 1.03)	0.90 (0.79, 1.03)
Exposure at work:				
Never at work	186896	637	1.0	1.0
Occasional	362062	1210	1.00 (0.90, 1.10)	0.99 (0.89, 1.09)
Regular	210505	621	0.89 (0.79, 0.99)	0.87 (0.78, 0.98)
Exposure at home:				
Never at home	424368	1374	1.0	1.0
Occasional	207918	721	1.05 (0.95, 1.15)	1.06 (0.97, 1.17)
Regular	126169	402	0.98 (0.88, 1.10)	1.02 (0.90, 1.14)
Years with someone who smokes:				
Never or less than 1 year	384292	1243	1.0	1.0
1–4 years	83662	290	1.09 (0.96, 1.24)	1.09 (0.96, 1.24)
5–9 years	65670	215	0.96 (0.83, 1.11)	0.98 (0.84, 1.13)
10–19 years	135986	423	0.96 (0.86, 1.07)	0.96 (0.86, 1.08)
20 – 29 years	121069	404	0.95 (0.85, 1.07)	0.96 (0.85, 1.08)
30 – 39 years	66210	249	0.93 (0.80, 1.07)	0.97 (0.84, 1.13)
40+ years	13605	50	0.96 (0.72, 1.28)	0.99 (0.74, 1.32)
P for trend:			0.17	0.24
Index of passive smoking:				
Neither at work nor at home	139088	449	1.0	1.0
Occasional exposure at home or work of <20 years	279151	921	1.09 (0.97, 1.22)	1.09 (0.97, 1.22)
Occasional exposure at home or work of ≥20 years	87259	296	0.97 (0.83, 1.12)	1.00 (0.86, 1.16)
Regular exposure at home or work of <20 years	89980	263	0.99 (0.85, 1.16)	0.99 (0.85, 1.16)
Regular exposure at home or work of ≥20 years	54846	180	0.96 (0.81, 1.14)	0.97 (0.81, 1.16)

*Adjusted for age (continuous), family history of breast cancer (yes, no), history of benign breast disease (yes, no), BMI (continuous), BMI at age 18 (continuous), height (continuous), alcohol consumption (0, 0.1–4.9, 5–14.9, ≥15 grams/day), age at menarche (≤11, 12, 13, 14, ≥15 years), parity (0, 1, 2, 3, ≥4), age at first birth (nulliparous, ≤24 years, 25–29 years, 30–34 years, ≥35 years), physical activity (<1, 1–<2, 2–<4, 4–<7, ≥7 hours/week), OC use (never, ever for <1 year, ever for 1–4 years, ever for 5–10 years, ever for >10 years), menopausal status (premenopause, postmenopause, dubious), postmenopausal hormone use (never, past for <5 years, past for ≥5 years, current for <5 years, current for ≥5 years), and age at menopause (continuous). Passive smoking at home and passive smoking at work were adjusted for each other. Exposure to parental smoking in childhood was adjusted for in analysis on passive smoking in adulthood.