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Original article

Tobacco

Pooled analysis of active cigarette smoking and invasive breast cancer risk in 14 cohort studies

Mia M Gaudet,[1]* Brian D Carter,[1] Louise A Brinton,[2] Roni T Falk,[2] Inger T Gram,[3] Juhua Luo,[4] Roger L Milne,[5] Sarah J Nyante,[2,6] Elisabete Weiderpass,[3,7,8,9] Laura E Beane Freeman,[2] Dale P Sandler,[10] Kim Robien,[11] Kristin E Anderson,[12] Graham G Giles,[5] Wendy Y Chen,[13,1] Diane Feskanich,[13] Tonje Braaten,[3] Claudine Isaacs,[15,16] Lesley M Butler,[1] Woon-Puay Koh,[18] Alicja Wolk,[19] Hans-Olov Adami,[7,20] Emily White,[21,22] Karen L Margolis,[23] Michael J Thun,[1] and Susan M Gapstur[1]

[1]Epidemiology Research Program, American Cancer Society, Atlanta, GA, USA, [2]Division of Cancer Epidemiology and Genetics, National Cancer Institute, Rockville, MD, USA, [3]Department of Community Medicine, Faculty of Health Sciences, UiT The Arctic University of Norway, Tromsø, Norway, [4]Department of Epidemiology and Biostatistics, School of Public Health, Indiana University, Bloomington, IN, USA, [5]Cancer Epidemiology Centre, Cancer Council Victoria, Melbourne, VIC, Australia and Centre for Epidemiology and Biostatistics, Melbourne School of Population and Global Health, The University of Melbourne, Victoria, Australia, [6]Department of Radiology, University of North Carolina, Chapel Hill, NC, USA, [7]Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden, [8]Cancer Registry of Norway, Institute of Population-Based Cancer Research, Oslo, Norway, [9]Genetic Epidemiology Group, Folkhälsan Research Center, Helsinki, Finland, [10]Epidemiology Branch, National Institute of Environmental Health Sciences, NIH/DHHS, Research Triangle Park, NC, USA, [11]Department of Epidemiology and Biostatistics, Milken Institute School of Public Health, George Washington University, Washington, DC, USA, [12]School of Public Health, University of Minnesota, Minneapolis, MN, USA, [13]Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA, [14]Department of Medical Oncology, Dana Farber Cancer Institute, Boston, MA, USA, [15]Department of Oncology, School of Medicine, Georgetown University, Washington, DC, USA, [16]Lombardi Comprehensive Cancer Center at Georgetown University, Washington, DC, USA, [17]University of Pittsburgh Cancer Institute, Pittsburgh, PA, USA, [18]Duke-NUS Graduate Medical School Singapore, Singapore, Saw Swee Hock School of Public Health, National University of Singapore, Singapore, Singapore, [19]Department of Environmental Medicine, Karolinska Institute, Stockholm, Sweden, [20]Department of Epidemiology, Harvard T.H. Chan School of Public Health Community, Boston, MA, USA, [21]Fred Hutchinson Cancer Research Center, Seattle, Washington, USA, [22]Department of Epidemiology, University of Washington, Seattle, Washington, USA and [23]HealthPartners Institute for Education and Research, Minneapolis, MN, USA

*Corresponding author. American Cancer Society, 250 Williams Street NW, Atlanta, GA 30303, USA.
E-mail: mia.gaudet@cancer.org

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Abstract

Background: The 2014 US Surgeon General's report noted research gaps necessary to determine a causal relationship between active cigarette smoking and invasive breast cancer risk, including the role of alcohol consumption, timing of exposure, modification by menopausal status and heterogeneity by oestrogen receptor (ER) status.

Methods: To address these issues, we pooled data from 14 cohort studies contributing 934 681 participants (36 060 invasive breast cancer cases). Cox proportional hazard regression models were used to calculate multivariable-adjusted hazard ratios (HRs) and 95% confidence intervals (CIs).

Results: Smoking duration before first birth was positively associated with risk (*P*-value for trend $= 2 \times 10^{-7}$) with the highest HR for initiation >10 years before first birth (HR = 1.18, CI 1.12–1.24). Effect modification by current alcohol consumption was evident for the association with smoking duration before first birth (P-value$=2\times10^{-4}$); compared with never-smoking non-drinkers, initiation >10 years before first birth was associated with risk in every category of alcohol intake, including non-drinkers (HR = 1.15, CI 1.04–1.28) and those who consumed at least three drinks per day (1.85, 1.55–2.21). Associations with smoking before first birth were limited to risk of ER+ breast cancer (P-value for homogeneity$=3\times10^{-3}$). Other smoking timing and duration characteristics were associated with risk even after controlling for alcohol, but were not associated with risk in non-drinkers. Effect modification by menopause was not evident.

Conclusions: Smoking, particularly if initiated before first birth, was modestly associated with ER+ breast cancer risk that was not confounded by amount of adult alcohol intake. Possible links with breast cancer provide additional motivation for young women to not initiate smoking.

Key words: tobacco smoking, alcohol, breast cancer

Key Messages

- In a pooled analysis of 14 prospective cohort studies of nearly one million women, smoking >10 years before first birth was associated with an 18% higher risk of breast cancer, the strongest association of all the smoking characteristics compared with never smokers.
- The association with smoking varied by alcohol consumption, but was evident in every category of alcohol intake. Smoking >10 years before first birth was associated with an 85% higher risk of breast cancer in the heaviest smokers and drinkers.
- Associations with years of smoking initiation were stronger for risk of ER+ breast cancer, estimates ranging from 1.02 to 1.21, than for risk of ER– breast cancer, estimates ranging from 0.95 to 1.08.
- The association of smoking characteristics with breast cancer risk varied little by menopausal status and age at menopause.

Introduction

Determining whether there is a causal relationship between active cigarette smoking and breast cancer risk has been controversial. There are biological data linking active smoking, particularly at young ages, with breast carcinogenesis, which include the induction of mammary cancers by 20 tobacco smoke compounds in rodents[1–3] and detectable tobacco metabolites,[4,5] and smoking-specific DNA adducts and p53 mutation in human breasts,[6–10] although limitations and inconsistencies do exist.[11] Despite the biological data and the positive associations in a large number of epidemiologic studies published before 2012,[1,2,11–16] the recent US Surgeon General's report concluded that 'the evidence is suggestive but not sufficient to

infer a causal relationship between active smoking and breast cancer'.[11] The report noted lingering epidemiological issues concerning the assessment of this relationship, including whether the association is due to: (i) the timing of exposure at early ages and/or long duration of smoking, (ii) confounding or effect modification by alcohol intake, (iii) modification by menopausal status or (iv) differences by oestrogen receptor (ER) status.

The two prevailing concerns are residual confounding by alcohol intake and timing of smoking initiation relative to first birth.[1,2,11–16] Alcohol consumption is an established risk factor for breast cancer; even consumption at low levels is associated with increased risk.[17] Some have argued that the association with active smoking can only be evaluated in never drinkers because of the potential correlation between cigarette smoking and alcohol consumption.[18] The Collaborative Group on Hormonal Factors in Breast Cancer concluded that there was no association of ever smoking [relative risk (RR)=1.03, 95% confidence interval (CI) 0.98–1.07]; however, among drinkers, the RR with ever smoking was 1.09 (95% CI 1.05–1.13), which was attenuated to 1.05 (95% CI 1.01–1.09) after adjustment for amount of alcohol consumed.[18] However, some of the recent studies[19–21] published after the Surgeon General's report have found associations with smoking even among non-drinkers when these women were examined separately. Analysis of smoking initiation relative to first birth is also an important issue because, before the first full-term birth, the undifferentiated breast epithelium is particularly susceptible to carcinogens.[22] Whereas previous cohort studies have shown that the strongest smoking association with breast cancer risk is among women who initiated smoking prior to first birth,[19–21,23–26] no studies have examined associations of initiation relative to first birth stratified by alcohol consumption.

In this study, we pooled data from 14 prospective cohorts and undertook a unified analytical approach to overcome the lingering epidemiological issues related to assessing the association between smoking and breast cancer risk.

Methods

Study population

Member studies of the National Cancer Institute (NCI) Cohort Consortium with smoking data and ≥500 incident breast cancer cases were invited to participate; 14 cohorts (Supplementary Table 1, available as Supplementary data at *IJE* online) agreed. Investigators from each cohort provided individual-level data for the entire cohort after excluding those who were male, had a personal history of cancer at baseline (except non-melanoma skin cancer), had missing information on smoking status at baseline or had other cohort-specific exclusions. Data for 934 681 women were included in this analysis. Written informed consent was obtained from study participants at entry into each cohort or was implied by participants' return of the enrolment questionnaire. The present investigation was approved by the Institutional Review Board (IRB) at each participating institution or was considered within the scope of the original IRB protocol.

Exposure information

De-identified data from the baseline questionnaire were provided for active cigarette smoking, current alcohol consumption (former alcohol drinkers were distinguished for only 6 of 14 studies) and other characteristics. Smoking status (never, former, current) is defined as at the time the baseline questionnaire was completed. Data were harmonized and variables were categorized a priori. Initiation of smoking relative to first birth, defined among parous women, is based on the number of years between age at smoking initiation and age at first pregnancy.

Case definition

In our primary analyses, cases were defined as incident, invasive breast cancers diagnosed after enrolment and identified through self-report, cancer registry linkage, medical record/pathology report or death certificate. In the latter situation, breast cancer had to be listed as a primary or contributory cause of death (ICD-9: 174 or ICD-O, ICD-10: C50). Incident *in situ* breast tumours were excluded from the case definition, because risk factors for *in situ* breast cancer might differ from invasive breast cancer.[27] Tumours of unknown invasiveness were assumed to be invasive.

Statistical analysis

Person-time was calculated from the date of the return of the baseline survey until the date of the first-occurring event: breast cancer diagnosis, death or last follow-up. Women diagnosed with carcinoma *in situ* of the breast were censored at the time of diagnosis. In pooled analyses, Cox proportional hazard regression models were used to calculate minimally adjusted and multivariable-adjusted hazard ratios (HRs) and 95% CI. All models controlled for study as a covariate and were stratified on age at enrolment. Multivariable-adjusted models included breast cancer risk factors (categorized as listed in Table 1, including categories for missing variables) and are shown with and without control for alcohol consumption. Models of time since quitting also included smoking duration. Linear trend

Table 1. Distribution of key factors as reported on the baseline survey, a pooled analysis of active smoking and invasive breast cancer risk among 14 cohorts in the NCI Cohort Consortium

	Never smoker (n = 494 194)	Former smoker (n = 288 895)	Current smoker (n = 151 592)
Years of follow-up, mean (SD)	13.5 (7.1)	12.2 (7.5)	14.7 (7.4)
Age at baseline, mean (SD)	54.1 (13.6)	55.5 (12.6)	49.7 (11.5)
Age at menarche, mean (SD)	12.8 (1.5)	12.8 (1.4)	12.9 (1.5)
Age at first birth, mean (SD)	24.4 (4.2)	24.2 (4.2)	23.4 (4.2)
Number of births, mean (SD)	2.5 (1.4)	2.4 (1.4)	2.4 (1.4)
Age at menopause, mean (SD)	48.1 (5.8)	47.6 (5.8)	46.7 (6)
Race (%)			
White	88.6	95.3	95.8
Black	2.2	2.4	1.8
Asian	7.4	1.0	1.7
Other/missing	1.8	1.4	0.8
Ethnicity (%)			
Not Hispanic	98.1	98.6	99.2
Hispanic	1.3	0.9	0.6
Missing	0.6	0.5	0.2
Education level (%)			
Less than high school	16.7	12.5	22.4
High school	19.3	19.5	21.5
Some college/college graduate	62.4	66.0	53.6
Missing	1.6	2.0	2.4
Parity (%)			
No	13.1	11.8	12.1
Yes	85.0	87.4	86.9
Missing	1.9	0.8	1.1
Family history of breast cancer (%)			
No	78.0	75.4	84.4
Yes	9.5	11.1	7.8
Missing	12.5	13.5	7.8
Benign breast disease (%)			
No	46.7	42.4	38.9
Yes	14.1	14.5	11.3
Missing	39.2	43.1	49.8
Ever oral contraceptive use (%)			
Never	50.6	46.2	43.0
Ever	46.9	52.1	54.7
Missing	2.5	1.7	2.4
Menopausal status (%)			
Pre-menopausal	31.5	27.5	43.2
Peri-menopausal	0.2	0.2	0.1
Post-menopausal	61.8	64.7	47.3
Missing	6.5	7.7	9.4
Ever post-menopausal hormone use (%)			
Never	62.1	54.1	69.3
Ever	32.3	41.3	26.1
Missing	5.7	4.6	4.6
Body mass index (kg/m^2, %)			
<18.5	1.9	1.3	3.3
18.5–22.4	26.9	25.1	35.0
22.5–24.9	24.2	24.2	25.7
25.0–29.9	27.9	29.0	23.9
30+	15.8	16.7	9.6
Missing	3.4	3.7	2.6

(continued)

Table 1. Continued

	Never smoker (n = 494 194)	Former smoker (n = 288 895)	Current smoker (n = 151 592)
Alcohol consumption at baseline (%)			
Not current drinker/non-drinker	39.6	20.0	23.2
<1 drink per day	39.7	49.9	54.9
1–2 drinks per day	4.9	7.8	6.7
>2 drinks per day	1.0	2.5	3.9
Current drinker, amount missing	14.7	19.8	11.3
Missing			
Oestrogen receptor status among cases			
Positive	67.6	69.0	63.7
Negative	14.7	13.9	14.2
Missing	17.7	17.2	22.1

tests were based on the *P*-value of the continuous smoking variables, excluding never smokers.[28] In addition to pooled analyses, a meta-analytic approach was used assuming a random effects model and weighting the cohorts based on the inverse of the cohort size. Between-study heterogeneity was assessed using the I^2 statistic,[29,30] in which I^2 of 0–40% was considered evidence of minimal heterogeneity, 30–60% moderate heterogeneity, 50–90% substantial heterogeneity and 75–100% considerable heterogeneity.[31]

Interaction analyses were conducted using a common reference group to evaluate for effect modification on the multiplicative scale. A *P*-value for interaction was calculated comparing the –2 log likelihood estimates of models with and without the interaction term(s). The interaction term was the cross-product of the two categorical variables with missing values excluded. Interaction analyses with menopausal status and age at menopause were conducted using a joint variable considering both exposures and excluded perimenopausal women. Associations were evaluated for subgroups defined by ER status using a joint Cox proportional hazards model.[32] Since data on ER status were not available for all cases, we compared main effect associations using cases with and without ER status to ensure those with data were not a biased sample. In sensitivity analysis, the influence of changes in smoking patterns prior to breast cancer diagnosis were examined by excluding cases that were diagnosed within the first two years of follow-up; this exclusion did not appreciably alter associations (data not shown). Reported *P*-values are two-sided. All programming was performed in R version 3.2.4 (3–10–2016), including the package survival (v2.38–3) for the aforementioned statistical models and the package forestplot (v1.4) for the forest plots.

Results

Among 934 681 study participants, 36 060 invasive breast cancer cases were diagnosed. The average age at baseline was 53.9 years, age at first birth was 24.0 years and number of births was 2.5. Most women were White (91.8%), had at least some college education (62.1%) and were post-menopausal at baseline (60.3%). Current smokers at baseline accounted for 16.2% of participants and they smoked an average of 15.3 cigarettes per day. Former smokers accounted for 30.9% of the participants and they quit smoking, on average, at 37.7 years of age. Most smokers (73.9%) started smoking before their first birth. Parous smokers who started before first birth, compared with those who started after first birth, were more likely to have smoked for longer (mean 23 vs 20 years, *P*-value $< 1\times10^{-3}$) and to have had their first birth at an older age (mean 24 vs 21 years of age, *P*-value $< 1\times10^{-3}$). Known breast cancer risk factors had expected associations (Supplementary Table 2, available as Supplementary data at *IJE* online).

Current smokers were more likely than never smokers to be less educated, pre-menopausal, current alcohol drinkers, oral contraceptive users, never users of menopausal hormone therapy and have a lower body mass index (BMI) (Table 1). Former smokers were more likely to have used menopausal hormone therapy than never smokers. Current and former smokers were more likely to drink alcohol at baseline than never smokers.

There was little confounding of the association between smoking status and invasive breast cancer (Table 2): controlling for alcohol intake at baseline changed the HR for current smoking from 1.09 to 1.07 (95% CI 1.04–1.10), compared with never smokers. There was only minimal evidence of between-study heterogeneity (Table 2 and Supplementary Figure 1, available as Supplementary data at *IJE* online). Associations of cigarettes per day and duration in current smokers and years since quitting and duration in former smokers showed linear trends (*P*-value < 0.02; Table 2); however, categorical HRs were within a narrow range of values (e.g. HRs for duration in current

Table 2. Multivariate-adjusted* hazard ratios (HRs) and 95% confidence intervals (CIs) for the association of smoking characteristics with invasive breast cancer risk, a pooled analysis among 14 cohorts in the NCI Cohort Consortium

	Cases	Rates	Age- and cohort-adjusted		Multivariable-adjusted* excluding alcohol intake		Multivariable-adjusted* including alcohol intake		I^2
			HR	95% CI	HR	95% CI	HR	95% CI	
Smoking status									
Never	18 647	254	1.00		1.00		1.00		
Former	11 585	296	1.11	(1.08, 1.13)	1.08	(1.06, 1.11)	1.06	(1.04, 1.09)	<1%
Current	5828	266	1.05	(1.02, 1.08)	1.09	(1.06, 1.13)	1.07	(1.04, 1.10)	39%
Cigarettes per day in current smokers									
Never smoker	18 647	254	1.00		1.00		1.00		
<10	1238	247	1.05	(0.99, 1.11)	1.10	(1.03, 1.16)	1.08	(1.01, 1.14)	47%
10–19	2033	260	1.04	(1.00, 1.09)	1.10	(1.04, 1.15)	1.07	(1.02, 1.13)	9%
20–29	1570	274	1.03	(0.97, 1.08)	1.06	(1.01, 1.12)	1.04	(0.98, 1.09)	15%
30–39	592	295	1.10	(1.02, 1.20)	1.13	(1.04, 1.22)	1.09	(1.00, 1.18)	27%
≥40	315	314	1.19	(1.07, 1.33)	1.22	(1.09, 1.37)	1.17	(1.05, 1.31)	<1%
P-value for linear trend[a]						2×10^{-3}		4×10^{-3}	
Years of smoking in current smokers									
Never smokers	18 647	254	1.00		1.00		1.00		
<10	94	248	0.93	(0.76, 1.15)	1.02	(0.83, 1.25)	1.01	(0.82, 1.23)	55%
10–19	794	250	1.10	(1.02, 1.19)	1.13	(1.05, 1.22)	1.11	(1.03, 1.20)	<1%
20–39	3632	274	1.04	(1.00, 1.08)	1.09	(1.05, 1.13)	1.06	(1.02, 1.10)	5%
≥40	1231	242	1.08	(1.02, 1.15)	1.12	(1.05, 1.19)	1.09	(1.03, 1.16)	10%
P-value for linear trend[a]						9×10^{-3}		0.02	
Years of smoking in former smokers									
Never smoker	18 647	254	1.00		1.00		1.00		
<5	1588	264	1.04	(0.99, 1.09)	1.04	(0.99, 1.10)	1.03	(0.98, 1.09)	<1%
5–10	1541	290	1.08	(1.03, 1.14)	1.05	(1.00, 1.11)	1.04	(0.98, 1.09)	<1%
10–20	3263	305	1.14	(1.10, 1.19)	1.11	(1.07, 1.15)	1.09	(1.05, 1.13)	<1%
20–30	2314	323	1.11	(1.06, 1.16)	1.08	(1.04, 1.13)	1.06	(1.02, 1.11)	<1%
30–40	1592	348	1.15	(1.09, 1.21)	1.12	(1.06, 1.18)	1.09	(1.04, 1.15)	<1%
>40	541	231	1.18	(1.08, 1.29)	1.17	(1.08, 1.28)	1.14	(1.05, 1.24)	<1%
P-value for linear trend[a]						1×10^{-4}		8×10^{-4}	
Years since quitting in former smokers									
Never smoker	18 647	254	1.00		1.00		1.00		
≥31	2251	318	1.08	(1.03, 1.13)	1.05	(1.00, 1.09)	1.03	(0.98, 1.07)	35%
21–30	3357	300	1.11	(1.07, 1.15)	1.09	(1.05, 1.13)	1.07	(1.03, 1.11)	26%
11–20	3815	290	1.14	(1.10, 1.18)	1.13	(1.09, 1.17)	1.11	(1.07, 1.15)	<1%
1–10	5828	266	1.05	(1.02, 1.09)	1.10	(1.06, 1.13)	1.07	(1.04, 1.11)	42%
P-value for linear trend[a]						3×10^{-4}		1×10^{-3}	
Age of smoking initiation in ever smokers									
Never smoker	18 647	254	1.00		1.00		1.00		
<16	1523	283	1.10	(1.04, 1.16)	1.03	(0.98, 1.09)	1.01	(0.96, 1.07)	<1%
16–20	10 251	290	1.10	(1.07, 1.12)	1.10	(1.07, 1.12)	1.07	(1.04, 1.10)	31%
21–25	3956	293	1.12	(1.08, 1.16)	1.13	(1.09, 1.17)	1.11	(1.07, 1.15)	<1%
≥25 years	1373	256	0.99	(0.94, 1.04)	1.02	(0.97, 1.08)	1.01	(0.95, 1.06)	<1%
P-value for linear trend[a]						0.02		0.07	
Smoking initiation relative to first birth in ever parous smokers									
Never smoker	16 025	250	1.00		1.00		1.00		
After first birth	1767	246	0.99	(0.95, 1.04)	1.07	(1.02, 1.12)	1.05	(1.00, 1.11)	<1%
≤5 years before birth	5913	270	1.03	(1.00, 1.07)	1.08	(1.04, 1.11)	1.06	(1.02, 1.09)	34%
6–10 years before birth	5201	302	1.16	(1.12, 1.20)	1.12	(1.09, 1.16)	1.10	(1.06, 1.14)	55%
>10 years before birth	2065	328	1.35	(1.29, 1.41)	1.20	(1.15, 1.26)	1.18	(1.12, 1.24)	36%
P-value for linear trend[a]						1×10^{-8}		2×10^{-7}	

*Multivariable-adjusted models included age, cohort, race/ethnicity, education, birth year, family history of breast cancer, history of benign breast disease, ever use of oral contraceptives, menopausal status and age at menopause, age at menarche, ever use of menopausal hormone therapy, age at first birth and number of live births, body mass index, and amount and frequency of alcohol use.

[a]Linear trend was evaluated using a continuous version of the variable excluding never smokers.

smokers ranged from 1.01 to 1.11). There was minimal heterogeneity between studies for most of the categories of these aforementioned smoking characteristics ($I^2 < 40\%$) with the exception of the lowest exposure categories of cigarettes per day (I^2=47%) and duration in current smokers (I^2=55%). Smoking 40 or more cigarettes per day at baseline had the strongest association with risk of breast cancer (HR=1.17, 95% CI 1.05–1.31; *P* for trend=4×10^{-3}).

Age of smoking initiation in ever smokers was not associated with breast cancer risk (Table 2). However, in parous women, those who initiated smoking more than 10 years before their first birth had the highest risk of breast cancer compared with never smokers (HR=1.18, 95% CI 1.12–1.24; Table 2). These results had only minimal evidence of between-study heterogeneity (Table 2 and Supplementary Figure 2, available as Supplementary data at *IJE* online). To evaluate whether this association was driven by residual confounding from later age at first birth or longer smoking duration, we conducted stratified analyses by these factors and found similar effects for smoking initiation in each strata (*P*-values for interaction=0.51 and 0.74, respectively; Supplementary Table 3a and b, available as Supplementary data at *IJE* online).

Smoking patterns differed by current alcohol consumption (results not otherwise shown): among non-drinkers, 68% of women were never smokers, 12% were current smokers and 20% were former smokers. Among people who drank more than two drinks per day, 28% were never smokers, 33% were current smokers and 39% were former smokers. Smoking for ≥40 years was more prevalent among women who reported drinking more than two drinks per day than not currently drinking: 11.5% vs 4.1%, respectively.

The associations of smoking characteristics of timing and duration with breast cancer risk were modified by current alcohol intake (*P*-values for interaction < 0.05; Table 3). Using a common reference group of never smokers, non-drinkers, former and current smoking was not associated with breast cancer risk among non-drinkers; however, current drinkers consuming two or more drinks per day who were former (HR=1.33, 95% CI 1.19–1.49) or current smokers (HR=1.32, 95% CI 1.16–1.49) were at slightly greater risk than expected under a multiplicative model (expected HRs=1.22 and 1.22, respectively). Smoking more than 10 years before first birth was associated with breast cancer risk among non-drinkers (HR=1.15, 95% CI 1.04–1.28) and in every stratum of alcohol intake (Table 3). Current drinkers consuming at least three drinks per day who smoked >10 years prior to first birth (HR=1.85, 95% CI 1.55–2.21; Table 3) were at noticeably greater risk than expected under a multiplicative model (expected HR=1.43).

Interactions with menopausal status and age at menopause were also examined (Supplementary Table 4, available as Supplementary data at *IJE* online). The associations with smoking status and smoking initiation relative to first birth did not meaningfully vary by menopause status and age at menopause.

We also examined whether the association with smoking status was different for subtypes defined by ER status (Table 4). Most breast cancers were ER + (67.4%); the association of smoking characteristics of timing and duration with breast cancer risk overall was similar for those with and without hormone receptor data (results not shown). The association with smoking before first birth differed by ER status, in which the association was stronger for risk of ER+ breast cancer than risk of ER– breast cancer (*P*-value for tumour heterogeneity=3×10^{-3}). Modification of the associations of smoking initiation relative to first birth with breast cancer risk by alcohol intake also was stronger for risk of ER+ breast cancer (data not in tables). Current drinkers consuming two or more drinks per day who smoked >10 years prior to first birth (HR=2.02, 95% CI 1.64–2.49) were also at greater risk than expected under a multiplicative model (expected HR=1.50).

Discussion

In this large pooled analysis, we addressed the key lingering epidemiologic issues raised in the 2014 US Surgeon General's report,[11] including the importance of duration and timing of smoking initiation, the role of alcohol intake, modification by menopausal status and differences in risk by ER status. We confirmed modest associations of current and former smoking with invasive breast cancer risk. We also showed that the timing of smoking initiation was the smoking characteristic most strongly associated with risk, with initiation more than 10 years before first birth associated with an 18% increased risk of breast cancer among parous ever smokers, and was evident in non-drinkers and in every stratum of alcohol intake. Those who both initiated smoking more than 10 years before first birth and who were the heaviest drinkers (two or more drinks per day) were at greatest risk from early smoking initiation (85% higher risk of breast cancer) compared with never-smoking non-drinkers. Furthermore, this association was stronger for risk of ER+ breast cancer.

Based on their meta-analysis of 22 case–control and prospective studies,[11] the Surgeon General's report concluded that the association for smoking before and after first birth did not differ. In our pooled analysis, we found a dose response with the number of years parous women smoked before their first birth. The association was evident in all strata of age at first birth and of duration of smoking,

Table 3. Multivariate-adjusted* hazard ratios (HRs) and 95% confidence intervals (CIs) for the association of smoking characteristics with invasive breast cancer risk by amount of alcohol intake, a pooled analysis among 14 cohorts in the NCI Cohort Consortium

	Non-current drinker			<1 drink per day			1–2 drinks per day			≥3 drinks per day			*P*-values for interaction
Cases	HR	95% CI	Cases	HR	95% CI	Cases	HR	95% CI	Cases	HR	95% CI		
Smoking status													
Never smoker	7746	1		8075	1.01	(0.98, 1.05)	1110	1.06	(0.99, 1.14)	303	1.21	(1.06, 1.38)	0.03
Former	2396	1.01	(0.97, 1.06)	6239	1.09	(1.05, 1.13)	1415	1.25	(1.18, 1.34)	528	1.33	(1.19, 1.49)	
Current	1262	1.01	(0.95, 1.08)	3207	1.11	(1.06, 1.16)	556	1.21	(1.11, 1.33)	417	1.32	(1.16, 1.49)	
Cigarettes per day in current smokers													
Never smoker	7746	1		8075	1.01	(0.98, 1.05)	1110	1.06	(0.99, 1.15)	303	1.2	(1.04, 1.38)	0.02
<10	225	0.94	(0.82, 1.07)	763	1.11	(1.02, 1.20)	116	1.4	(1.16, 1.69)	38	1.43	(1.03, 2.00)	
10–19	437	1.1	(0.99, 1.21)	1188	1.11	(1.04, 1.19)	169	1.19	(1.01, 1.39)	71	1	(0.78, 1.29)	
20–29	366	0.95	(0.86, 1.06)	815	1.07	(1.00, 1.16)	166	1.18	(1.01, 1.38)	147	1.3	(1.08, 1.56)	
30–39	139	1	(0.85, 1.18)	266	1.15	(1.02, 1.31)	79	1.22	(0.97, 1.53)	82	1.28	(1.01, 1.62)	
≥40	85	1.18	(0.95, 1.47)	121	1.17	(0.97, 1.40)	24	0.89	(0.59, 1.33)	79	1.85	(1.45, 2.36)	
P-value for linear trend[a]		0.16			0.07			0.55			4×10^{-3}		
Years of smoking in current smokers													
Never smoker	7746	1		8075	1.01	(0.98, 1.05)	1110	1.06	(0.98, 1.14)	303	1.19	(1.03, 1.37)	0.03
<10	29	1.25	(0.87, 1.80)	49	0.92	(0.7, 1.23)	3	0.63	(0.20, 1.96)	1	0.35	(0.05, 2.51)	
10–19	188	1.11	(0.96, 1.29)	499	1.15	(1.04, 1.26)	46	1.09	(0.81, 1.46)	27	1.09	(0.74, 1.60)	
20–39	725	0.96	(0.89, 1.04)	2097	1.11	(1.05, 1.17)	338	1.15	(1.03, 1.30)	282	1.31	(1.13, 1.51)	
≥40	294	1.07	(0.95, 1.21)	545	1.07	(0.97, 1.17)	146	1.45	(1.23, 1.72)	99	1.42	(1.13, 1.79)	
P-value for linear trend[a]		0.25			0.12			3×10^{-3}			7×10^{-3}		
Years of smoking in former smokers													
Never smoker	7746	1		8075	1.02	(0.98, 1.05)	1110	1.06	(0.98, 1.14)	303	1.2	(1.04, 1.38)	
<5	380	1	(0.90, 1.10)	950	1.08	(1.01, 1.16)	112	1.06	(0.87, 1.28)	35	1.06	(0.75, 1.50)	
5–10	312	1.03	(0.92, 1.15)	883	1.02	(0.95, 1.10)	174	1.33	(1.14, 1.55)	68	1.54	(1.20, 1.99)	
10–20	586	0.99	(0.91, 1.08)	1876	1.13	(1.07, 1.19)	388	1.34	(1.20, 1.49)	153	1.35	(1.13, 1.62)	
20–30	444	1	(0.91, 1.10)	1265	1.12	(1.06, 1.20)	268	1.14	(1.01, 1.30)	103	1.13	(0.91, 1.40)	
30–40	357	1.1	(0.99, 1.23)	751	1.08	(1.00, 1.17)	212	1.29	(1.12, 1.48)	100	1.46	(1.17, 1.82)	
>40	124	1.1	(0.92, 1.32)	214	1.08	(0.94, 1.24)	80	1.59	(1.27, 1.99)	44	1.59	(1.16, 2.18)	2×10^{-4}
P-value for linear trend[a]		0.01			0.04			0.36			0.43		
Years since quitting smoking in former smokers													
Never smoker	7746	1		8075	1.01	(0.98, 1.05)	1110	1.06	(0.99, 1.14)	303	1.2	(1.05, 1.38)	0.05
≥31	474	1.02	(0.93, 1.12)	1209	1.05	(0.98, 1.11)	276	1.22	(1.08, 1.38)	95	1.19	(0.95, 1.47)	
21–30	634	0.97	(0.89, 1.05)	1914	1.09	(1.04, 1.15)	378	1.25	(1.12, 1.39)	168	1.47	(1.24, 1.74)	
11–20	789	1.07	(0.99, 1.15)	2177	1.14	(1.09, 1.2)	377	1.25	(1.13, 1.40)	190	1.31	(1.12, 1.54)	
1–10	1262	1.01	(0.95, 1.07)	3207	1.11	(1.06, 1.16)	556	1.21	(1.10, 1.32)	417	1.31	(1.16, 1.48)	
P-value for linear trend[a]		0.02			1×10^{-3}			0.48			0.95		
Age of smoking initiation in ever smokers													
Never smoker	7746	1		8075	1.02	(0.98, 1.05)	1110	1.06	(0.98, 1.13)	303	1.2	(1.05, 1.37)	

(continued)

Table 3. Continued

		Non-current drinker		<1 drink per day			1–2 drinks per day			≥3 drinks per day			*P*-values for interaction
Cases	HR	95% CI	Cases	HR	95% CI	Cases	HR	95% CI	Cases	HR	95% CI		
<16	327	1.04	(0.93, 1.16)	817	1.01	(0.94, 1.09)	128	1.13	(0.95, 1.35)	84	1.34	(1.06, 1.69)	
16–20	2046	1.03	(0.98, 1.08)	5576	1.08	(1.04, 1.12)	1243	1.3	(1.22, 1.39)	639	1.35	(1.21, 1.50)	
21–25	776	0.96	(0.90, 1.04)	2294	1.2	(1.14, 1.26)	388	1.2	(1.08, 1.33)	155	1.32	(1.11, 1.57)	
≥25	399	1.03	(0.93, 1.14)	687	1.04	(0.96, 1.12)	120	1.12	(0.93, 1.34)	48	1.11	(0.83, 1.48)	5×10^{-6}
P-value for linear trend[a]		0.79			0.75			0.04			0.13		
Smoking initiation relative to first birth in parous ever smokers													
Never smoker	6697	1		7024	1.03	(1.00, 1.07)	860	1.05	(0.97, 1.14)	258	1.24	(1.08, 1.43)	2×10^{-4}
After first birth	497	1.01	(0.92, 1.10)	907	1.12	(1.04, 1.20)	125	1.13	(0.94, 1.35)	61	1.18	(0.91, 1.53)	
≤5 years before birth	1275	1	(0.94, 1.07)	3195	1.09	(1.05, 1.14)	591	1.24	(1.14, 1.36)	314	1.35	(1.18, 1.54)	
6–10 years before birth	963	1.05	(0.98, 1.12)	2977	1.14	(1.09, 1.19)	665	1.34	(1.23, 1.46)	301	1.33	(1.16, 1.52)	
>10 years before birth	386	1.15	(1.04, 1.28)	1163	1.19	(1.11, 1.27)	197	1.3	(1.12, 1.50)	148	1.85	(1.55, 2.21)	
P-value for linear trend[a]			0.06			6×10^{-4}			0.02			5×10^{-4}	

*Multivariable-adjusted models included age, cohort, race/ethnicity, education, birth year, family history of breast cancer, history of benign breast disease, ever use of oral contraceptives, menopausal status and age at menopause, age at menarche, ever use of menopausal hormone therapy, age at first birth and number of live births, body mass index and amount of alcohol use.

[a]Linear trend was evaluated using a continuous version of the variable excluding never smokers.

indicating that the association was independent of these factors, as previously suggested.[11] The inconsistencies among prior studies in the Surgeon General's report might be due to the small number of cases, especially if examining the number of years of smoking prior to first birth in individual studies and the recent maturity of prospective studies that included birth cohorts who initiated smoking at a young age. For example, recent publications from other cohorts (not included in our analysis) also support stronger associations among parous women who smoke before first birth in highly screened women,[25] in racial/ethnic subgroups[21,26] and a comparatively large analysis of Europeans.[19] Our pooled analysis included at least a portion of the data from six of the prospective studies included in the Surgeon General's report.[11] Our results for initiation years before first birth are also consistent with models of carcinogenesis of the breast.[22]

We further addressed the concern of residual confounding effects by alcohol intake on the association of smoking with breast cancer risk[1,2,11–16] by using statistical control in multivariable models and by stratifying the association into categories of alcohol intake with additional statistical control for amount of alcohol within categories. Statistical control for alcohol intake at baseline only slightly attenuated the RRs for smoking characteristics in our study. Consistently with the Collaborative Group on Hormonal Factors in Breast Cancer,[18] we observed no association between smoking status at baseline and breast cancer risk among non-drinkers. However, we did observe associations with initiating smoking more than 10 years prior to first birth in non-drinkers and in every stratum of alcohol intake at baseline. We cannot, however, eliminate the possibility that this association is further confounded by alcohol consumption during early adult life, which was not captured by the majority of the studies in our analysis. In the Nurses' Health Study II, women who had higher alcohol intake between menarche and first birth also reported higher intakes at baseline and after first pregnancy compared with women who abstained between menarche and first birth. In their multivariable analyses, alcohol intake before first birth, compared with those abstaining before first birth, was associated with breast cancer risk (per 10-g increase: HR=1.11, 95% CI 1.00–1.23), independently of cumulative alcohol intake after first pregnancy.[33]

Stronger associations between smoking and breast cancer in pre-menopausal women has been hypothesized because the morphology of the breast and endogenous hormone levels undergo significant changes during the menopausal transition and other breast cancer risk factors are modified by menopausal status.[11] However, we found no modification by menopausal status, which is consistent with prior studies.[34,35] In our analysis, smoking initiation

Table 4. Multivariate-adjusted* hazard ratios (HRs) and 95% confidence intervals (CIs) for the association of smoking characteristics with invasive breast cancer risk by oestrogen receptor (ER) status, a pooled analysis among 14 cohorts in the NCI Cohort Consortium

	ER+			ER−			*P*-value for homogeneity
	Cases	HR	95% CI	Cases	HR	95% CI	
Smoking status							
Never smoker	11 616	1		2563	1		0.05
Former	7297	1.08	(1.05, 1.11)	1455	0.99	(0.93, 1.06)	
Current	3466	1.05	(1.01, 1.10)	766	1	(0.92, 1.08)	
Cigarettes per day in current smokers							
Never smoker	11 616	1		2563	1		0.55
<10	708	1.07	(0.99, 1.16)	151	0.94	(0.80, 1.10)	
10–19	1121	1.03	(0.97, 1.09)	266	1.04	(0.92, 1.17)	
20–29	998	1.05	(0.98, 1.12)	215	0.98	(0.86, 1.13)	
30–39	388	1.11	(1.01, 1.23)	82	0.98	(0.78, 1.22)	
≥40	204	1.15	(1.00, 1.32)	49	1.18	(0.89, 1.56)	
P-value for linear trend[a]			0.03			0.11	
Years of smoking in current smokers							
Never smoker	11 616	1		2563	1		0.68
<10	51	1.05	(0.81, 1.36)	14	0.95	(0.56, 1.60)	
10–19	466	1.12	(1.01, 1.23)	113	1.02	(0.84, 1.24)	
20–39	2167	1.05	(1.00, 1.10)	509	1.01	(0.92, 1.11)	
≥40	742	1.06	(0.99, 1.14)	121	0.96	(0.81, 1.14)	
P-value for linear trend[a]			0.1			0.2	
Years of smoking in former smokers							
Never smoker	12 608	1		2740	1		
<5	1007	1.02	(0.95, 1.09)	235	1.02	(0.89, 1.16)	
5–10	1077	1.09	(1.02, 1.16)	206	0.91	(0.79, 1.04)	
10–20	2273	1.13	(1.08, 1.18)	445	0.98	(0.89, 1.09)	
20–30	1626	1.08	(1.02, 1.14)	317	1	(0.89, 1.13)	
30–40	1102	1.08	(1.01, 1.15)	227	1.14	(0.99, 1.30)	
>40	375	1.14	(1.02, 1.26)	75	1.27	(1.01, 1.60)	0.04
P-value for linear trend[a]				0.07			4×10^{-4}
Years since quitting smoker in former smokers							
Never smoker	11.616	1		2563	1		0.07
≥31	1441	1.06	(1.00, 1.12)	264	0.91	(0.81, 1.03)	
21–30	2147	1.1	(1.05, 1.15)	427	0.99	(0.90, 1.09)	
11–20	2345	1.1	(1.05, 1.15)	542	1.11	(1.02, 1.22)	
1–10	3466	1.05	(1.01, 1.09)	766	1	(0.92, 1.08)	
P-value for linear trend[a]			0.12			3×10^{-4}	
Age of smoking initiation in ever smokers							
Never smoker	12 608	1		2740	1		
<16	1018	1.01	(0.95, 1.08)	224	0.94	(0.82, 1.08)	
16–20	6927	1.08	(1.05, 1.12)	1425	0.99	(0.93, 1.06)	
21–25	2634	1.11	(1.06, 1.15)	569	1.08	(0.99, 1.19)	
≥25	923	1	(0.93, 1.07)	182	0.96	(0.82, 1.11)	0.16
P-value for linear trend[a]			0.07			0.28	
Smoking initiation relative to first birth in parous ever smokers							
Never smoker	9936	1		2239	1		3×10^{-3}
After first birth	1030	1.02	(0.96, 1.09)	226	1.06	(0.93, 1.20)	
≤5 years before birth	3548	1.05	(1.01, 1.09)	798	1.03	(0.95, 1.11)	
6–10 years before birth	3389	1.13	(1.09, 1.18)	644	0.95	(0.87, 1.04)	
>10 years before birth	1248	1.21	(1.14, 1.28)	271	1.08	(0.95, 1.22)	
P-value for linear trend[a]			5×10^{-7}			0.29	

*Multivariable-adjusted models included age, cohort, race/ethnicity, education, birth year, family history of breast cancer, history of benign breast disease, ever use of oral contraceptives, menopausal status and age at menopause, age at menarche, ever use of menopausal hormone therapy, age at first birth and number of live births, body mass index and amount of alcohol use.

[a]Linear trend was evaluated using a continuous version of the variable excluding never smokers.

prior to first birth and smoking status were not modified by menopausal status, which is consistent with the large cohort of European women.[19] Although the interaction was statistically significant for duration of smoking in current smokers, the lower risk estimated for the women who had smoked for ≥40 years and who had not gone through menopause was based on very few cases (n=26) and the adjacent exposure category of women who had smoked for 20–39 years did not differ across strata of menopause.

Despite initial published hypotheses and early evidence from small studies supporting a stronger association of smoking with ER– breast cancer,[11] the findings from our pooled analysis suggest smoking, particularly initiation >10 years prior to first birth, suggest a positive association with risk of ER+, but not ER–, breast cancer. Results from the large cohort study of European women[19] also suggested stronger positive associations with smoking for risk of hormone-receptor-positive disease. Although more recent data summarized in the Surgeon General's report found stronger associations for ER+ breast cancer, they listed a number of limitations among the published studies, including use of case–control data, incomplete control for confounders and bias due to incomplete assessment of ER status.[11] Our pooled analysis was based on prospective cohort data, we controlled for a large number of known breast cancer risk factors and we found no bias in the association with smoking among the cases who had ER status compared with those who did not.

Although data pooling provided a large number of study participants, it also presented limitations. Variables were harmonized to be inclusive of all participating cohorts, and we were not able to harmonize all variables. We were not able to define a reference group that excluded passive smokers or lifelong never drinkers, which likely biased our results toward the null. Despite this limitation, we did not find evidence of between-study heterogeneity in the associations (Supplementary Figures 1 and 2, available as Supplementary data at *IJE* online). We only collected baseline data on smoking status and covariate information. Although current smokers at baseline may have quit during follow-up, one of the studies included here did not find differences in results of baseline or updated smoking status.[23]

Consistently with previous studies published after the Surgeon General's report,[19,23,25,26,36] our estimate of the magnitude of association between smoking status and breast cancer risk is modest. However, this association did not appear to be confounded by alcohol intake; rather, our results support a synergistic relationship between smoking initiation and adult alcohol drinking. Furthermore, we found that longer duration of smoking prior to first birth was associated with risk, and this association persisted in both drinkers and non-drinkers. The associations with smoking were more consistently associated with risk of ER+ breast cancer. Other lingering epidemiologic issues mentioned in the recent US Surgeon General's report that we addressed in this manuscript do not appear to have a major influence. Whereas the association with breast cancer might be modest relative to the more profound health effects of smoking on lung and other cancers, the number of breast cancer cases attributable to smoking might increase over time, as the prevalence of adolescent smoking in the USA has remained stable since the 1930s[37,38] and globally smoking initiation at young ages is increasing[39] and a greater proportion of women are delaying childbirth.[40] Continued research in this area is warranted to further support public health campaigns aimed at preventing smoking and encouraging early cessation.

Supplementary Data

Supplementary data are available at *IJE* online.

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