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Active smoking and risk of estrogen receptor positive and triple-negative breast cancer among women 20–44 years of age

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Abstract

BACKGROUND—The evidence regarding the relationship between smoking and breast cancer among young women is mixed, and prior studies have not assessed if smoking is differentially associated with risks of the major breast cancer subtypes.

METHODS—We conducted a population-based case-control study consisting of 778 estrogen receptor positive (ER+) and 182 triple-negative (TN) invasive breast cancer cases 20-44 years of age diagnosed from 2004-2010 in the Seattle-Puget Sound metropolitan area, and 938 cancer-free controls. We assessed associations between various aspects of smoking history and risks of ER+ and TN breast cancer using polytomous logistic regression.

RESULTS—Ever smokers had a 1.3-fold [95% confidence interval (CI): 1.1-1.7] increased risk of breast cancer overall, and when stratified by cancer subtype they had a 1.4-fold (95% CI: 1.1-1.8) increased risk of ER+ breast cancer but no elevation in their risk of TN disease [odds ratio (OR) = 1.1, 95% CI: 0.7-1.6]. Current/recent smokers with a ≥10 pack-year history of smoking had a 1.6-fold (95% CI: 1.1-2.4) increased risk of ER+ breast cancer, but no increase in their risk of TN breast cancer (OR=1.0, 95% CI: 0.5-1.9).

CONCLUSIONS—Our results suggest that young women who are current/recent smokers with high pack-year histories may have an increased risk of ER+, but not TN, breast cancer. While this association is modest, our findings suggest that an increased risk of ER+ breast cancer may be another health risk incurred by young women who smoke.

Keywords

Breast cancer; smoking; estrogen receptor; triple-negative; premenopausal

Introduction

Numerous epidemiologic studies have investigated the relationship between smoking and breast cancer risk among young women, but they have yielded conflicting results. An IARC review based on 18 studies published through 2002 concluded that the existing data

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evaluating this association was inconclusive [1]. However, a more recent review of the literature estimated that current smokers have a 15% to 40% increased risk of premenopausal breast cancer [2]. Of the more recent studies conducted since the IARC review, seven [3-9] of the ten observed a positive association between smoking and premenopausal breast cancer, with the three not finding a relationship limited by comparatively smaller sample sizes [10-12].

An important gap in the existing literature is a lack of information on how smoking influences risk of different molecular subtypes of breast cancer. The most common subtypes are estrogen receptor-positive (comprising the luminal A and B subtypes), while one of the most aggressive subtypes is triple-negative breast cancer (TNBC) [tumors that lack estrogen receptor (ER), progesterone receptor (PR), and HER2-neu (HER2) expression, and the majority of them have the so-called basal-like phenotype] [13]. The unique molecular characteristics of the different subtypes along with the considerable variability in their prognosis suggest that they likely have unique etiologies. Two prior studies have evaluated the association between smoking and breast cancer risk in young premenopausal women only according to ER/PR status [8, 9], though neither included HER2. One of these studies found smoking intensity and duration to be positively associated with risk of ER+, but not ER- breast cancer [9], while the other found that smoking increases risk of premenopausal breast cancer risk similarly across ER/PR subtypes [8]. Studies focused on young women are of particular interest because TNBC accounts for a higher proportion of cases among young women than it does among older, postmenopausal women [14]. Also, active smoking is one of the few potentially modifiable risk factors for breast cancer among young women. Therefore, further characterizing the relationship between smoking and breast cancer risk is of public health importance. Toward this goal, we evaluated the association between smoking and different molecular subtypes of breast cancer risk in a population-based case-control study of women 20-44 years of age.

Materials and Methods

The design and overall methods employed in this study have been described previously.[15, 16] Briefly, we conducted a population-based case-control study in the three county Seattle-Puget Sound metropolitan area (King, Pierce, and Snohomish counties) among women 20 to 44 years of age designed specifically to characterize risk factors for breast cancer among young women diagnosed with invasive breast cancer. Potentially eligible cases diagnosed between January 2004 and June 2010 with no prior history of *in situ* or invasive breast cancer were identified thorough the Cancer Surveillance System (CSS), the population-based tumor registry that serves the 13 counties of Western Washington state and participates in the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute (Bethesda, MD). Of the 1,359 eligible cases identified, 1,056 (78%) were interviewed. Of those not enrolled (n=303), 82% refused to be interviewed, 10% could not be located, and 8% died before interview could be conducted. In addition to basic information on breast cancer diagnosis, we obtained information on a variety of tumor characteristics from the cancer registry and from a centralized review of pathology reports. This includes data on tumor histology and estrogen receptor (ER), progesterone receptor (PR), and HER2-neu (HER2) status. ER and PR positivity were defined as positive staining

of ≥1% of cells and negativity as 0 to <1 % positive staining of cells. HER2 positivity was based on an immunohistochemistry (IHC) score of 3+ and/or a FISH-positive result and negativity was defined as an IHC score of 0 or 1+ and/or a FISH-negative result. Cases with a 2+ HER2 IHC result without a FISH result were considered to have an inconclusive and therefore unknown HER2 status. This information was used to group cases into three groups: ER+ (approximating the luminal subtypes), ER-/PR-/HER2- (triple-negative cases approximating the basal-like subtype) and ER-/HER2+ (approximating the HER2-overexpressing subtype). This approach has been used in several other studies focused on characterizing risk factors for different molecular subtypes of breast cancer [17-19]. The 60 ER-/HER2+ (5.7%) were excluded from this analysis because we had insufficient statistical power to evaluate risks specific to this case type. Additionally excluded were the 28 cases (2.7%) for whom data on ER, PR, and/or HER2 status were missing.

A population-based control group was identified and recruited using random digit dialing. Controls were frequency matched within 5-year age groups to the cases using one-step recruitment. We used a combination of list-assisted (purchased randomly generated telephone numbers) and Mitofsky-Waksberg (telephone numbers randomly generated ourselves using a clustering factor of 5) [20] random digit dialing to identify potential controls from the general population of female residents of King, Pierce, and Snohomish counties. Of the 1,489 eligible controls identified, 943 (63%) were interviewed.

Data Collection

The study protocol was approved by the Fred Hutchinson Cancer Research Center Institutional Review Board, and written informed consent was obtained from all study subjects. Cases and controls were interviewed in-person and asked about their reproductive history, demographics, body size, physical activity, alcohol drinking, medical history, breast cancer screening, and family history of breast cancer.

In addition, detailed information about smoking history, including recency, ages when smoked, average number of cigarettes smoked per day, and years since quitting smoking (if applicable) were obtained. Our questioning was limited to exposures that occurred before each participant's reference date. The reference date used for each woman with breast cancer was her diagnosis date. Control reference dates were assigned to reflect the expected distribution of reference dates among the cases. The mean time between reference date and interview date was 18 months for cases and 20 months for controls, and the median times were 16 months and 19 months, respectively. This was consistent with our goal of trying to interview women within two years of their reference date. Data on smoking were missing for five controls and eight cases (six ER+ and two ER-/PR-/HER2- cases). Therefore, our final analytic data set consisted of 938 control women, 778 ER+ cases and 182 ER-/PR-/HER2- cases.

Statistical Analysis

Never smokers were defined as women who never smoked or smoked less than 100 cigarettes in their lifetime, and they served as the reference category in all analyses. Ever smokers were women who reported smoking 100 cigarettes or more in their

lifetime [11, 21, 22]. Ever smokers were queried on their smoking history with detailed information collected for each period of time women smoked at different frequencies including ages marking the beginning and ending of each period and the frequency and intensity of smoking during each period. Using this information we computed a series of variables related to smoking recency, duration, and intensity. Former smokers were women who quit smoking more than two years before the reference date, and current/recent smokers were defined as women who were active smokers within two years of their reference date. Duration of smoking was calculated based on ages women reported started and stopped smoking. Number of pack-years of smoking was calculated by determining the number of years women smoked one pack of cigarettes a day (1 pack is equal to 20 cigarettes). The number of years since women quit smoking was calculated as the difference between current age and the age at which they quit smoking for former smokers. The analytic categories of smoking we assessed were ever smoked (never / ever), recency (never / current or recent / former), total years smoked (never / <5.0 / 5.0-9.9 / 10.0-14.9 / ≥15.0), age first started smoking (never / ≤14 / 15-17 / ≥18), pack-year history (never / <2.5 / 2.5-4.9 / 5.0-9.9 / 10.0-14.9 / ≥15.0), years since quit smoking (never / <5 / 5-9.9 / ≥10), whether they began smoking before menarche (no / yes), and whether they began smoking before first birth (no / yes).

We used polytomous logistic regression to calculate odds ratios (ORs) and their associated 95% confidence intervals (CIs) to compare ER+ breast cases and triple-negative breast cancer cases to controls. All analyses were conducted using Stata/SE version 12.1 (StataCorp LP, College Station, TX). All models were adjusted for age (five year categories) and reference year (continuous) since controls were matched to cases on these factors. Several potential confounders and effect modifiers of the relationship between smoking and breast cancer risk were assessed including: education, household income, race/ethnicity, use of oral contraceptives, mammography screening history, first-degree family history of breast cancer, body mass index (BMI) one year prior to reference date, age at menarche, number of full-term pregnancy, parity number, age at first live birth, alcohol consumption, and physical activity. Only age at first live birth changed our risk estimates by more than 10% when added to the model, so our final statistical models were adjusted for age, reference year, and age at first live birth. None of these factors were found to be statistically significant effect modifiers based on likelihood ratio testing (all p-values for interaction were >0.05). Dose-response relationships were tested by treating each exposure category as a continuous variable exclusive of the never smokers. We conducted Wald tests to estimate differences in risk between our ER+ and ER-/PR-/HER2- case groups.

Results

Compared to control women, cases as a whole were somewhat more likely to have first-degree family history of breast cancer, to be nulliparous, and to ever have had a screening mammogram (Table 1). Compared to the ER+ breast cancer cases, the TNBC cases were somewhat more likely to be younger, to be African American, to be less highly educated, to have first-degree family history of breast cancer, to have a BMI ≥30.0 kg/m^2, to have used oral contraceptives for 10 years or longer, to have a younger age at first live birth, and to have less history of screening mammogram. The differences with respect to race, first-

degree family history of breast cancer, parity number, age at first livebirth, and screening mammogram were statistically significant ($p<0.05$).

Compared to never smokers, ever smokers had a 30% (95% CI: 1.1-1.7) increased risk of breast cancer overall with similar results for current and former smokers (Table 2). Risk did not vary appreciably by total years smoked, the age women first started smoking, or timing of smoking initiation with respect to ages at menarche or first live birth. There was some evidence that women with the shortest and longest pack-year histories of smoking had particularly elevated risks of breast cancer, but the p-value for trend was non-significant. The elevations in breast cancer risk associated with smoking were primarily limited to increases in risk of ER+ breast cancer as the observed risk estimates were generally higher for ER+ and essentially null for TN breast cancer, but the test for heterogeneity across case groups were not statistically significant. There was also evidence that risk returned to baseline among former smokers who had not smoked for 10 years or longer for ER+ breast cancer.

In analyses stratified by smoking recency, among current/recent smokers there was some suggestion that longer smoking and pack-year histories were associated with greater risks of ER+ breast cancer. Specifically, current/recent smokers who had smoked for 15 or more years and those with a 10 or more pack-year history had 50% and 60% increased risks, respectively, of ER+ breast cancer, compared to those with shorter numbers of years smoked and pack years (Table 3). Again though, neither duration nor pack-year history of smoking was related to risk of TN breast cancer among current/recent smokers, but the tests for heterogeneity across case groups were not statistically significant.

Discussion

This study adds to recent evidence [2] indicating that smoking is modestly associated with breast cancer risk in young women. Expanding on prior work, our findings suggest that this association is limited to an increase in risk of ER+ breast cancer, and that smoking does not impact risk of TNBC. While no prior studies have evaluated the relationships between smoking and risk of different breast cancer subtypes defined by joint ER/PR/HER2 status in young women, two evaluated risk according to ER/PR status [8, 9]. Consistent with our results, in the only other study focused exclusively on younger women, limited to women 25-42 years of age, having smoked for at least 20 years was associated with a 37% increased risk of ER+ breast cancer but was not associated with risk of ER- breast cancer [8]. Studies including broader age ranges have also reported that ever smoking is associated with a 22-42% increased risk of ER+ breast cancer, but is not associated with ER- breast cancer [23, 24]. Risk of ER+ breast cancer was increased 5% per 20 pack-year history of smoking, but with only a 2% increased risk of ER- breast cancer and there were no differences of risk between pre- and postmenopausal women [8]. Two studies have evaluated the relationship between smoking and breast cancer risk by ER/PR/HER2 status. In the large Women's Health Initiative prospective cohort of postmenopausal women, smoking duration and intensity were positively associated with risk of ER+, but not TNBC, as women with a ≥40 pack-year history of smoking had a 24% increased risk of ER+ breast cancer but no increase in risk of TNBC [22]. A population-based case-control study conducted in Atlanta

including women 20-54 years of age, which did not stratify results by age or menopausal status, observed that former smokers had a 37% increased risk of ER+/PR+/HER2-, a 140% increased risk of ER+/PR+/HER2+, and a 56% increased risk of TNBC [25]. Current smokers had an 89% increased risk of ER-/PR-/HER2+ breast cancer, but risks of ER+ and TN breast cancer subtypes were reduced 39-69%[25]. With the exception of this latter study, overall, our results are consistent with the majority of prior studies evaluating risk by receptor subtype in finding that various aspects of smoking are positively related to risk of ER+ breast cancer, but not to risk of ER- breast cancer subtypes.

The biologic mechanisms underlying the potential relationship between smoking and ER+ breast cancer may relate to the estrogenic effects of smoking. There are a large host of carcinogens in tobacco smoke such as polycyclic aromatic hydrocarbons (PAHs), aromatic amines, and nitrosoamines that could promote breast cancer [1]. These substances have been detected in the breast fluid and tissue of smokers, and [26] these carcinogens can have both estrogenic [27] and anti-estrogenic effects [28-30]. PAHs share structural similarities with estrogen, and can potentially have both anti-estrogenic and estrogenic effects [31]. However, in a premenopausal population, any anti-estrogenic effect of active smoking is likely insufficient to overcome high endogenous circulating estrogen levels [8]. The estrogenic effects of substances from active smoking have been demonstrated in experimental studies such as cigarette smoke condensates activating estrogen receptors in breast cancer cells [27]. Other components of cigarette smoke, including 2-hydroxyfluorene, 2-hydroxyphenanthrene, and n-propyl-p-hydroxybenzoate, also exhibited estrogenic activity in a yeast system that expresses human estrogen receptor [32]. These result suggests that active smoking could contribute to the increase in risk of ER+ breast cancer observed [8, 9] as the substances and metabolites of tobacco smoke carcinogens are detectable in the breast fluid and breast tissue of active smokers [33, 34].

It is important to acknowledge the limitations of this study. Given our case-control design, recall bias is a potential concern with potential for differential recall by case-control status. However, recall of smoking history is generally high [21] and the mean time between reference date and interview date was 18 months so women were in general asked to recall exposure histories that were not too far in the past. Confounding is another potential concern. However, we carefully assessed a wide range of potential confounders to inform our final statistical models. The comparatively small number of triple negative breast cancer cases included in this study hampered our statistical power to characterize the relationship between smoking and risk of this breast cancer subtype. However, no prior studies have evaluated the association between smoking and breast cancer risk in young women according to combined ER/PR/HER2 and so our results warrant confirmation in larger studies. Another concern is that we did not observe dose-response effects with smoking duration or intensity potentially reducing the robustness of our results. However, our results are consistent with several other studies [8, 22-25] and the association is biologically plausible [1, 8, 26-34].

This study suggests that smoking history, in particular longer term recent smoking, is associated with a modest increase in risk of ER+ breast cancer, but not with risk of TN breast cancer. Given the numerous adverse health effects of smoking, an increased risk of

breast cancer in young women has now consistently been observed to be another risk. Thus on-going efforts to prevent the initiation of smoking and to promote smoking cessation are clearly warranted.

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Table 1

Distribution of selected characteristics among controls and cases, ER+, ER-/PR-/HER2- breast cancer.

	Control		Cases						
			Total		Subtypes [a]				
	(n = 938)		(n = 960)		ER+ [b] (n = 778)		ER-/PR-/HER2-(n = 182)		
Characteristic	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**p-value [*]**
Age (years)									
20-29	25	2.7%	22	2.3%	15	1.9%	7	3.8%	
30-34	86	9.2%	77	8.0%	55	7.1%	22	12.1%	
35-39	267	28.5%	257	26.8%	199	25.6%	58	31.9%	
40-44	560	59.7%	604	62.9%	509	65.4%	95	52.2%	0.05
Reference (years)									
2004-2005	306	32.6%	273	28.4%	212	27.2%	61	33.5%	
2006-2007	360	38.4%	330	34.4%	273	35.1%	57	31.3%	
2008-2010	272	29.0%	357	37.2%	293	37.7%	64	35.2%	0.002
Race/ethinicity									
Non-Hispanic white	767	81.9%	749	78.4%	607	78.5%	142	78.0%	
African American	34	3.6%	49	5.1%	32	4.1%	17	9.3%	
Asian/Pacific Islannder	82	8.8%	113	11.8%	99	12.8%	14	7.7%	
Native American	19	2.0%	26	2.7%	19	2.5%	7	3.8%	
Hispanic White	35	3.7%	18	1.9%	16	2.1%	2	1.1%	< 0.001
Missing	1		5		5		0		
Education									
High school or less	98	10.4%	113	11.8%	89	11.4%	24	13.2%	
Post high-school/some college	305	32.5%	318	33.1%	253	32.5%	65	35.7%	
College graduate	354	37.7%	352	36.7%	283	36.4%	69	37.9%	
Graduate/Professional school	181	19.3%	177	18.4%	153	19.7%	24	13.2%	0.5
First-degree family history of breast cancer									
No	814	89.9%	742	80.0%	602	80.3%	140	78.7%	
Yes	91	10.1%	186	20.0%	148	19.7%	38	21.3%	< 0.001
Missing	33		32		28		4		

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	Control		Cases						
			Total		Subtypes [a]				
	(n = 938)		(n = 960)		ER+ [b] (n = 778)		ER-/PR-/HER2-(n = 182)		
Characteristic	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**p-value [*]**
BMI (kg/m^2)									
<25.0	532	57.0%	571	59.7%	473	61.0%	98	54.1%	
25.0-29.9	232	24.8%	226	23.6%	182	23.5%	44	24.3%	
≥30.0	170	18.2%	159	16.6%	120	15.5%	39	21.5%	0.2
Missing	4		4		3		1		
Duration of oral contraceptives use (years)									
Never	103	11.0%	107	11.2%	92	11.9%	15	8.4%	
<5.0	338	36.1%	340	35.7%	281	36.3%	59	33.0%	
5.0-9.9	218	23.3%	194	20.4%	155	20.0%	39	21.8%	
≥10	276	29.5%	312	32.7%	246	31.8%	66	36.9%	0.3
Missing	3		7		4		3		
Parity number									
Nulliparous	191	20.4%	259	27.0%	209	26.9%	50	27.5%	
1	193	20.6%	192	20.0%	158	20.3%	34	18.7%	
2	365	38.9%	351	36.6%	283	36.4%	68	37.4%	
≥3	189	20.1%	157	16.4%	127	16.3%	30	16.5%	0.05
Missing	0		1		1		0		
Age at first livebirth among parous women (years)									
<25	218	29.2%	225	32.2%	168	29.6%	57	43.2%	
25-29	225	30.1%	222	31.8%	187	33.0%	35	26.5%	
30-34	204	27.3%	173	24.7%	143	25.2%	30	22.7%	
≥35	100	13.4%	79	11.3%	69	12.2%	10	7.6%	0.04
Missing	0		2		2		0		
Age at menarche (years)									
<12	190	20.3%	214	22.3%	170	21.9%	44	24.2%	
12-13	519	55.4%	538	56.1%	438	56.4%	100	54.9%	
≥14	227	24.3%	207	21.6%	169	21.8%	38	20.9%	0.6
Missing	2		1		1		0		

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	Control		Cases						
			Total		Subtypes [a]				
	(n = 938)		(n = 960)		ER+ [b] (n = 778)		ER-/PR-/HER2-(n = 182)		
Characteristic	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**p-value [*]**
Alcohol consumption (average number of alcohol drinks / week)									
Never	227	24.3%	220	23.1%	175	22.7%	45	24.9%	
0-1.4	234	25.1%	223	23.4%	189	24.5%	34	18.8%	
1.4-3.7	235	25.2%	245	25.7%	196	25.4%	49	27.1%	
≥3.7	237	25.4%	265	27.8%	212	27.5%	53	29.3%	0.6
Missing	5		7		6		1		
Ever had a screening mammogram									
Never	478	51.0%	399	41.6%	315	40.5%	84	46.2%	
Ever	460	49.0%	561	58.4%	463	59.5%	98	53.8%	<0.001

Abbreviations: BMI, body mass index. ER, estrogen receptor. PR, progesterone receptor. HER2, human epidermal growth factor receptor 2.

[*] Chi-squared.

[a] ER-/HER2+ were excluded because of limited number (60 cases).

[b] Regardless of PR/HER2 status.

Table 2

Association of active smoking and breast cancer risk.

	Control (n = 938)		All case (n = 960)				ER+ (n = 778) [a]				ER-/PR-/HER2-(n = 182)				*P for heterogeneity* ER-/PR-/HER2- vs ER+
	n	%	n	%	OR [b]	95% CI	n	%	OR [b]	95% CI	n	%	OR [b]	95% CI	
Smoking status at reference date															
Never	639	68.1%	606	63.1%	1.0	(Reference)	495	63.6%	1.0	(Reference)	111	61.0%	1.0	(Reference)	
Ever (current/former)	299	31.9%	354	36.9%	1.3 [c]	1.1 - 1.7	283	36.4%	1.4 [c]	1.1 - 1.8	71	39.0%	1.1	0.7 - 1.6	0.2
Current / recent	139	14.8%	160	16.7%	1.4 [c]	1.0 - 1.9	123	15.8%	1.4 [c]	1.0 - 2.0	37	20.3%	1.2	0.7 - 2.1	0.4
Former	160	17.1%	194	20.2%	1.3	1.0 - 1.7	160	20.6%	1.4 [c]	1.0 - 1.8	34	18.7%	0.9	0.6 - 1.5	0.2
Total years smoked (years)															
<5.0	39	4.2%	54	5.6%	1.6	1.0 - 2.6	42	5.4%	1.6	1.0 - 2.7	12	6.6%	1.5	0.7 - 3.4	
5.0-9.9	54	5.8%	74	7.7%	1.3	0.9 - 2.0	60	7.7%	1.4	0.9 - 2.2	14	7.7%	1.0	0.5 - 2.1	
10.0-14.9	54	5.8%	54	5.6%	1.2	0.8 - 1.8	41	5.3%	1.2	0.8 - 1.9	13	7.1%	1.1	0.5 - 2.4	
≥15.0	149	15.9%	170	17.7%	1.3	1.0 - 1.8	138	17.8%	1.4 [c]	1.0 - 1.9	32	17.6%	1.0	0.6 - 1.7	
p for trend without never smoker					0.7				0.8				0.7		0.9
Age at first smoking (years)															
≥18	110	11.7%	119	12.4%	1.3	0.9 - 1.8	95	12.2%	1.3	0.9 - 1.9	24	13.2%	1.2	0.7 - 2.2	
15-17	109	11.6%	140	14.6%	1.3	1.0 - 1.8	111	14.3%	1.4 [c]	1.0 - 1.9	29	15.9%	1.1	0.6 - 1.9	
≤14	80	8.5%	95	9.9%	1.3	0.9 - 1.9	77	9.9%	1.5	1.0 - 2.2	18	9.9%	0.8	0.4 - 1.7	
p for trend without never smoker					0.9				0.7				0.4		0.2
Pack-years															
<2.5	98	10.9%	126	13.3%	1.5 [c]	1.1 - 2.1	100	13.1%	1.5 [c]	1.1 - 2.1	26	14.5%	1.4	0.8 - 2.4	
2.5-4.9	34	3.8%	36	3.8%	1.3	0.7 - 2.2	29	3.8%	1.4	0.8 - 2.4	7	3.9%	0.9	0.3 - 2.4	
5.0-9.9	25	2.8%	46	4.9%	0.9	0.5 - 1.4	36	4.7%	1.0	0.6 - 1.6	10	5.6%	0.6	0.2 - 1.5	
10.0-14.9	29	3.2%	35	3.7%	1.2	0.7 - 2.1	26	3.4%	1.2	0.7 - 2.2	9	5.0%	1.3	0.5 - 3.3	
≥15.0	72	8.0%	95	10.1%	1.6 [c]	1.1 - 2.3	79	10.3%	1.7 [c]	1.1 - 2.5	16	8.9%	1.2	0.6 - 2.3	
p for trend without never smoker					0.9				0.9				0.7		0.9
Years since quit smoking for the former smokers (years)															
<10	50	6.3%	67	8.4%	1.5	1.0 - 2.4	55	8.4%	1.7 [c]	1.1 - 2.7	12	8.3%	1.1	0.5 - 2.4	
≥10	110	13.8%	126	15.8%	1.2	0.9 - 1.6	104	15.9%	1.2	0.9 - 1.7	22	15.2%	0.9	0.5 - 1.6	

	Control (n = 938)		All case (n = 960)				ER+ (n = 778) [a]				ER-/PR-/HER2-(n = 182)				*P for heterogeneity* ER-/PR-/HER2- vs ER+
	n	**%**	**n**	**%**	**OR [b]**	**95% CI**	**n**	**%**	**OR [b]**	**95% CI**	**n**	**%**	**OR [b]**	**95% CI**	
p for trend without never smoker					0.2				0.2				0.4		0.8
Began smoking before menarche															
No	277	29.5%	327	34.1%	1.3 [c]	1.1 - 1.7	259	33.3%	1.4 [c]	1.1 - 1.8	68	37.4%	1.1	0.8 - 1.7	0.4
Yes	22	2.3%	27	2.8%	1.1	0.6 - 2.1	24	3.1%	1.4	0.7 - 2.7	3	1.6%	0.2	0.03 - 1.9	0.08
Began smoking before first livebirth (among parous women only)															
Never	509	68.1%	432	61.7%	1.0	(Reference)	348	61.3%	1.0	(Reference)	84	63.6%	1.0	(Reference)	
No	15	2.0%	15	2.1%	1.1	0.5 - 2.4	8	1.4%	0.8	0.3 - 2.0	7	5.3%	2.0	0.8 - 5.3	0.2
Yes	223	29.9%	253	36.1%	1.3 [c]	1.1 - 1.7	212	37.3%	1.4 [c]	1.1 - 1.8	41	31.1%	1.0	0.7 - 1.5	0.1

Abbreviations: ER, estrogen receptor. PR, progesterone receptor. HER2, human epidermal growth factor receptor 2. OR, odds ratio. CI, confidence interval.

[a] Regardless of PR/HER2 status.

[b] ORs are adjusted by age, reference year, and age at first livebirth.

[c] $P < 0.05$.

Table 3

Association of active smoking and breast cancer risk stratified by current / recent versus former smoking status.

	Never vs. current / recent smokers														
	Control (n = 778)		**Case (n = 766)**				**ER+ (n = 618)** [a]				**ER-/PR-/HER2- (n = 148)**				
	n	**%**	**n**	**%**	**OR** [b]	**95% CI**	**n**	**%**	**OR** [b]	**95% CI**	**n**	**%**	**OR** [b]	**95% CI**	***P for heterogeneity* ER-/PR-/HER2- vs ER+**
Total years smoked (years)															
Never	639	82.2%	606	79.1%	1.0	(Reference)	495	80.1%	1.0	(Reference)	111	75.0%	1.0	(Reference)	
<15.0	25	3.2%	29	3.8%	1.5	0.8 - 3.0	17	2.8%	1.2	0.6 - 2.7	12	8.1%	2.0	0.8 - 5.0	
≥15.0	113	14.5%	131	17.1%	1.4	1.0 - 1.9	106	17.2%	1.5 [c]	1.1 - 2.1	25	16.9%	1.0	0.5 - 1.7	
p for trend without never smoker					0.9				0.6				0.2		0.5
Pack-years															
<10.0	55	7.1%	67	8.8%	1.3	0.8 - 2.1	46	7.5%	1.3	0.8 - 2.1	21	14.2%	1.4	0.7 - 2.9	
≥10.0	79	10.2%	91	11.9%	1.4	1.0 - 2.1	75	12.2%	1.6 [c]	1.1 - 2.4	16	10.8%	1.0	0.5 - 1.9	
p for trend without never smoker					0.9				0.7				0.3		0.7
	Never vs. former smokers														
	Control (n = 799)		Case (n = 800)				ER+ (n = 655) [a]				ER-/PR-/HER2- (n = 145)				
	n	%	n	%	OR [b]	95% CI	n	%	OR [b]	95% CI	n	%	OR [b]	95% CI	
Total years smoked (years)															
Never	639	80.2%	606	75.9%	1.0	(Reference)	495	75.8%	1.0	(Reference)	111	76.6%	1.0	(Reference)	
<15.0	122	15.3%	153	19.2%	1.3	1.0 - 1.8	126	19.3%	1.4 [c]	1.0 - 1.9	27	18.6%	1.0	0.5 - 1.7	
≥15.0	36	4.5%	39	4.9%	1.2	0.7 - 2.0	32	4.9%	1.2	0.7 - 2.2	7	4.8%	0.8	0.3 - 2.4	
p for trend without never smoker					0.6				0.6				0.7		0.9
Pack-years															
<10.0	131	16.5%	141	17.9%	1.2	0.9 - 1.6	119	18.5%	1.3	1.0 - 1.8	22	15.5%	0.8	0.5 - 1.4	
≥10.0	22	2.8%	39	5.0%	1.6	0.9 - 2.9	30	4.7%	1.5	0.8 - 2.9	9	6.3%	1.9	0.7 - 4.9	
p for trend without never smoker					0.5				0.7				0.2		0.97

Abbreviations: ER, estrogen receptor. PR, progesterone receptor. HER2, human epidermal growth factor receptor 2. OR, odds ratio. CI, confidence interval.

[a] Regardless of PR/HER2 status.

[b] ORs are adjusted by age, reference year, and age at first livebirth.

[c] $P < 0.05$.