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Active smoking and risk of Luminal and Basal-like breast cancer subtypes in the Carolina Breast Cancer Study

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Abstract

Purpose—Growing evidence suggests an association between active cigarette smoking and increased breast cancer risk. However, the weak magnitude of association and conflicting results have yielded uncertainty and it is unknown whether associations differ by breast cancer subtype.

Methods—Using population-based case–control data from phases I and II of the Carolina Breast Cancer Study, we examined associations between self-reported measures of smoking and risk of Luminal and Basal-like breast cancers. We used logistic regression models to estimate case–control odds ratios (OR) and 95 % confidence intervals (CI).

Results—Ever smoking (current and former) was associated with a weakly increased risk of Luminal breast cancer (OR 1.12, 95 % CI 0.92–1.36) and was not associated with risk of Basal-like breast cancer (OR 0.96, 95 % CI 0.69–1.32). Similarly, smoking duration of more than 20 years was associated with increased risk of Luminal (OR 1.51, 95 % CI 1.19–1.93), but not Basal-like breast cancer (OR 0.90, 95 % CI 0.57–1.43). When stratified by race, elevated odds ratios between smoking and Luminal breast cancer risk were found among black women across multiple exposure measures (ever smoking, duration, and dose); conversely, among white women odds ratios were attenuated or null.

Conclusions—Results from our study demonstrate a positive association between smoking and Luminal breast cancer risk, particularly among black women and women with long smoking histories. Addressing breast cancer heterogeneity in studies of smoking and breast cancer risk may elucidate associations masked in prior studies.

Keywords

Smoking; Breast cancer; Estrogen receptor; Luminal; Basal-like; Race

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Introduction

In a 2014 report on the health consequences of cigarette smoking, the US Surgeon General concludes that there is insufficient evidence to suggest a causal relationship between active smoking and breast cancer risk [1]. Indeed, epidemiologic studies of smoking and breast cancer risk have yielded mixed results. Because many breast cancers are estrogen dependent [2], studies that report earlier menopause and lower circulating levels of estrogen among smokers support an “anti-estrogenic” effect of smoking and would suggest inverse associations [3]. However, few epidemiologic studies have supported this hypothesis [4, 5]. Epidemiologic studies have more commonly suggested a positive association [6–9], consistent with tissue culture and animal experiments showing that cigarette smoke components disrupt cell-cycle regulation, cause DNA damage, and are linked to malignant transformation [10–12].

Adding complexity to studies of smoking and breast cancer risk is the observation that breast cancer is a heterogeneous disease defined by distinct and reproducible gene expression profiles [13]. These gene expression profiles have identified breast tumor “intrinsic subtypes” that are prognostic and predictive of response to treatment [14]. In addition, these subtypes have different patterns of risk factor associations [15], consistent with the categorization of breast cancers into at least two etiologic types [16]. Growing evidence suggests a possible link between smoking and the Luminal, hormone receptor positive (HR +) breast cancer types, ranging from a modest 5 % increased risk to more than doubled risk when comparing ever smokers with never smokers [6–9, 17–20]. Given that the associations between smoking and breast cancer may be subtype specific, and subtype prevalence varies by study, breast cancer heterogeneity may influence agreement between studies.

Using case–control data from phases I and II of the Carolina Breast Cancer Study, we describe associations between self-reported measures of smoking and risk of Luminal or Basal-like breast cancers. We also examine associations by race to determine whether smoking is linked to differential risk of either breast cancer subtype among black versus white women. By considering the heterogeneous nature of breast cancer, findings from this study may elucidate associations masked in prior investigations of smoking and breast cancer risk.

Methods

Study design

The Carolina Breast Cancer Study (CBCS) combines molecular biology and epidemiology to examine genetic and environmental risk factors for breast cancer [21]. Phases I and II of the population-based case–control study were conducted in 24 adjoining counties in central and eastern North Carolina from 1993–1996 and 1996–2001, respectively. The latter phase was included to increase sample size. Smoking exposures and study participant characteristics did not differ appreciably between the two phases.

Case selection

The present study includes women diagnosed with invasive breast cancer. CBCS cases were identified by a rapid case ascertainment system implemented through collaboration with the North Carolina Central Cancer Registry (NCCCR). To be eligible for inclusion as a case the patient must have been female and received a first diagnosis of invasive breast cancer between 1 May 1993 and 30 September 1995 (Phase I) or 1 May 1996 and 30 September 2001 (Phase II). The patient also must have resided in the 24-county study region and been between the ages of 20 and 74 at the time of diagnosis.

To facilitate identification of differences in breast cancer etiology by race and age, cases were selected using a randomized recruitment strategy that oversampled black and young women. The patient's treating physician was contacted to seek permission to invite the patient to participate in the study, yielding a case response rate of 76 %. In total, invasive cases included 787 black women and 1,016 white or non-black women.

Control selection

Population-based controls were selected using an incidence density sampling strategy and frequency-matched to cases by 5-year age group, race, and county of residence. Women aged 20–64 years old were identified through the North Carolina Division of Motor Vehicle records; those aged 65 years and older were identified through Medicare claims records. Women were invited to participate in the study by mail, yielding a control response rate of 55 %. In total, controls matched to invasive cases included 718 black women and 846 white or non-black women; and controls matched to carcinoma in situ cases included 70 black women and 388 white or non-black women.

Exposure and outcome assessments

In accordance with regulations outlined by the Institutional Review Board at the University of North Carolina at Chapel Hill School of Medicine, cases and controls provided informed consent to participate in an in-person nurse-administered interview, which included anthropometric measurements and blood sample collection. Nurses used a standard questionnaire to obtain information on family history of cancer; menstrual and reproductive history; weight and body size recall during youth and early adulthood; occupational exposures; physical activity engagement; alcohol use; smoking history; exogenous hormone use; and socioeconomic status. Anthropometric measurements were taken in duplicate to obtain weight (lbs), height (inches), waist (cm), and hip circumference (cm).

Smoking exposure

Active smokers were defined as women who reported smoking 100 cigarettes or more during their lifetimes. Women were also asked to report age at smoking initiation and, where applicable, age at smoking cessation. On average, interviews were conducted 6 months following case ascertainment. Since a breast cancer diagnosis is likely to influence decisions concerning smoking cessation, we defined current smokers as women who self-reported smoking at the time of interview and women who reported smoking cessation at the same age of case/control selection. Former smokers were defined as women who quit at any age prior to the age at case/control selection. These data were used to derive smoking duration

(years), years since smoking cessation, and categories of smoking initiation relative to age at menarche and/or age at first full-term pregnancy. Women with a history of smoking were also asked to estimate the number of cigarette packs smoked per day.

Breast cancer outcome

Cases provided informed consent that allowed CBCS investigators to obtain medical records, pathology reports, and paraffin-embedded tumor blocks through coordination with the hospital where surgery was to be performed. For invasive cases, estrogen receptor (ER) positivity and progesterone receptor (PR) positivity were obtained from the patient's medical records. Tumor blocks were sectioned and stained for three additional immunohistochemical (IHC) markers to define breast cancer molecular subtype; these markers include human epidermal growth factor receptor-2 (HER2); human epidermal growth factor receptor-1 (HER1); and cytokeratin 5/6 (CK5/6). Assay procedures and cut points for positivity have been described, previously [22, 23]. IHC staining was performed at the IHC Core Laboratory, University of North Carolina. Luminal breast cancers were defined as (ER+ and/or PR+, regardless of HER2 status), and Basal-like tumors were defined as (ER−, PR−, HER2−, HER1+ and/or CK5/6+).

Other measures

Race was based on self-report and the majority of women self-identified as black or white. Less than 2 % of women self-identified as Native American, Asian, mixed, or other race (n = 53). We described study participants as black or white and combined the small number of women who did not self-identify as black or white with analyses of white study participants; notably, excluding non-black and non-white women from our analyses did not result in substantially different race-specific associations between smoking and breast cancer risk. Age was self-reported at time of case/control selection. Women aged <50 were defined as postmenopausal if they experienced natural menopause, bilateral oophorectomy, or had irradiation to the ovaries. For women aged ≥50, postmenopausal status was based on the cessation of menstruation by any means. All other women were assigned as being premenopausal. Women were considered to have a first-degree family history of breast cancer if their biological mother or a full female sibling had been diagnosed with breast cancer. Alcohol use was defined as recent, former, or never, relative to age at case/control selection. Oral contraceptive use was defined by four categories of usage: never, <5, 5–10, or >10 years. Women were defined as parous if they reported ever having a live birth or having a pregnancy that lasted 7 months or more. Breastfeeding behavior was defined using three categories, according to the age when the study participant first experienced breastfeeding: never, ≤24, ≥25. Age at menarche was defined as the age the woman experienced onset of a regular menstrual cycle. Body mass index (BMI = body weight (kg)/height $(m)^2$) was categorized according to cut points outlined by the National Heart, Lung, and Blood Institute (NHLBI) (<25 normal or underweight, 25–29 overweight, ≥30 obese). Hormone replacement therapy use was defined as ever or never. And age at first birth was characterized as <25 or ≥25 years.

Data analysis

We examined the relationship between smoking exposure and risk of invasive breast cancer, according to race and breast cancer molecular subtype. We used unconditional logistic regression with polytomous outcomes and 95 % confidence intervals to estimate the association between smoking exposure and breast cancer risk. To evaluate heterogeneity across subtype-specific odds ratios, we reported *p* values for likelihood ratio tests that compared case-only models with or without each smoking measure as an explanatory value and used a statistical significance level of alpha = 0.05. All odds ratios were adjusted for randomized recruitment probabilities using an offset term. Potential confounders were selected and adjusted for based upon literature review and directed acyclic graph analysis. These variables included age, family history, alcohol use, menopausal status, hormone replacement therapy use, oral contraceptive use, parity, age at first birth, age at first breastfeeding, age at menarche, and BMI. All analyses were conducted using SAS 9.4 (SAS Institute Inc, Cary, NC).

Results

Table 1 describes characteristics of breast cancer cases and controls in the Carolina Breast Cancer Study. Compared to controls, cases were more likely to have a first-degree family history of breast cancer and were also more likely to be nulliparous. Fewer cases were postmenopausal compared to controls and a fewer cases had a body mass index of 25 or greater. Cases and controls did not differ appreciably with respect to alcohol use, oral contraceptive use, age at menarche, or age at first breastfeeding (among parous women).

Smoking measures, their associated case–control odds ratios, and 95 % confidence intervals are presented in Table 2. Overall, history of ever smoking was associated with a weakly increased risk of breast cancer (OR 1.07, 95 % CI 0.92–1.25). Smoking status, defined as current, former, or never, and smoking dose, defined as the number of cigarette packs smoked per day, also showed weakly positive associations with overall breast cancer risk. The strongest association was observed for smokers with duration of smoking greater than 20 years compared to non-smokers (OR 1.33, 95 % CI 1.09–1.61). The relationship between long smoking duration (>20 years) and breast cancer risk persisted when limiting the analysis to either current (OR 1.22, 95 % CI 0.97–1.53) or former smokers (OR 1.54, 95 % CI 1.15–2.07). Current smokers were more likely than former smokers to have smoking histories that totaled 20 years or greater (67 vs. 30 %). In addition, former smokers who quit 5–10 years prior to case/control selection had increased risk of breast cancer (OR 1.39, 95 % CI 1.01–1.93). Smoking initiation following adolescence (>20 years old) was associated with a small increase in risk (OR 1.07, 95 % CI 0.89–1.28). Further, smoking initiation relative to menarche and first full-term pregnancy were not associated with increased risk of breast cancer. Specifically, we did not observe an appreciable association between smoking and breast cancer risk for: (1) smoking initiation prior to menarche; (2) smoking initiation after menarche and ≥11 years before first full-term pregnancy; or (3) smoking initiation after menarche and <11 years before first full-term pregnancy.

Table 3 presents smoking measures and case–control odds ratios for Luminal and Basal-like subtypes. Compared with never smokers, ever smokers had a slight increased risk of

Luminal type breast cancer (OR 1.12, 95 % CI 0.92–1.36) and a weakly decreased odds ratio for Basal-like breast cancer (OR 0.96, 95 % CI 0.69–1.32). Smoking more than 20 years (OR 1.51, 95 % CI 1.19–1.93) was associated with increased risk of Luminal breast cancer subtype. For smoking intensity of one or more cigarette packs per day, we observed an inverse association with the Basal-like breast cancer type (OR 0.47, 95 % CI 0.25–0.89). In general, strata of time since smoking cessation did not show a consistent pattern of association with risk of Luminal or Basal-like breast cancer risk. Similar to results for overall breast cancer risk, smoking initiation following the adolescent period (>20 years of age) was associated with a slight increased risk of Luminal disease (OR 1.18, 95 % CI 0.88–1.57). Our tests of heterogeneity demonstrated statistically different odds ratios for the Luminal and Basal-like subtypes for smoking dose ($p = 0.02$) and duration ($p = 0.00$).

In Table 4, we extended the subtype-specific analyses to explore differences by race. Among black women, the magnitudes of the case–control odds ratios were substantially greater than those observed for white women. Current smoking (OR 1.53, 95 % CI 1.04–2.26) and long smoking duration (OR 2.06, 95 % CI 1.38–3.06) were associated with increased risks of Luminal type breast cancer among black women; however, current smoking (OR 0.91, 95 % CI 0.65–1.26) and long smoking duration (OR 1.31, 95 % CI 0.96–1.79) had weaker associations with Luminal breast cancer risk among white women. For the Basal-like breast cancer type, former smoking was associated with increased risk among black women (OR 1.71, 95 % CI 1.02–2.86) and smoking dose was associated with inverse risk among white women (OR 0.38, 95 % CI 0.16–0.90). Our tests of heterogeneity demonstrated statistically different odds ratios for the Luminal and Basal-like subtypes for smoking status ($p = 0.02$) and duration ($p = 0.06$) among black women and smoking dose ($p = 0.10$) among white women.

Discussion

In this paper, we describe associations between active smoking and breast cancer risk in the Carolina Breast Cancer Study [21]. Using a case–control study design, we report a weakly increased risk of breast cancer for women who were ever smokers (current and former) and a more pronounced increase in risk among women who smoked more than 20 years. This finding differed by race, where long smoking duration (>20 years) was associated with higher risk of breast cancer for black women, but not white women. Our subtype-specific analyses demonstrated that both current smoking and long smoking duration were associated with increased risk of Luminal breast cancers, but not Basal-like breast cancers—where subtypes were defined by the joint expression of the estrogen receptor, progesterone receptor, and three other immunohistochemical (IHC) markers used to determine breast cancer intrinsic subtype [24]. Subtype specificity of smoking-associated risk persisted when examining tumors by hormone receptor and triple-negative status, as current and long-term smoking were associated with HR-positive (HR+) breast tumors, but not HR-negative (HR−) or triple-negative breast tumors. By examining breast cancer heterogeneity, results from this study may elucidate associations masked in prior investigations of smoking and breast cancer risk.

At present, there is no consensus on whether smoking is associated with breast cancer risk. We observed a weak risk increase (~7 %) among women who were classified as “ever smokers” and a slightly higher risk increase (~12 %) when examining the association between “ever smokers” and the Luminal breast cancer type. Our observed associations are weaker than those reported by Kawai et al., who demonstrated a 30 % increased risk of any breast cancer and a 40 % increased risk of ER + breast cancer among “ever smokers” in a population-based case–control study of women in the Seattle Puget-Sound metropolitan area [18]. Notably, none of the smoking measures considered by Kawai et al. were associated with the Basal-like or ER− breast cancer types. However, in our study we observed inverse associations between smoking dose and Basal-like breast cancer risk, with evidence for statistically significant heterogeneity of the subtype-specific ORs for dose and duration. These observations suggest that active smoking may be both quantitatively and qualitatively associated with increased risk of Luminal disease and inverse risk of Basal-like breast tumors. Nevertheless, a number of previous studies have reported positive associations between smoking and ER− breast tumors [19, 25–27], while others have reported null associations between smoking and either subtype (i.e., ER+ and ER−) [28, 29] or inverse associations between smoking and the ER+ subtype [30]. It is important to note that these studies vary in population, study design, and the specific smoking measures used for their analyses.

The heterogeneous nature of breast cancer is well established with the identification of distinct and reproducible “intrinsic subtypes” that predict prognosis and response to treatment; however, less is known concerning the utility of these subtypes in studies of etiology [14, 16]. Breast cancer incidence trends have been used to suggest the existence of two main etiologic types—the Luminal and Basal-like types—based on estrogen receptor expression and average age at onset. Basal-like breast cancers are ER− and have an early average age at onset relative to Luminal breast cancers, which are ER+ and have a later average age at onset [16, 31, 32]. These observations, together with results from previous studies of breast cancer etiology, support arguments that breast cancers of Luminal epithelial and basal/myoepithelial origins represent two distinct diseases with distinct risk factor profiles [15]. Thus, if the relationship between smoking and breast cancer risk is specific to the Luminal breast cancer type and has no association with the Basal-like breast cancer type, characterizing breast cancer as a homogenous disease in studies of etiology results in outcome misclassification and may bias effect measure estimates, as evidenced by the attenuated case–control odds ratios observed in our study [33].

The empirical induction period between smoking initiation and breast cancer diagnosis is thought to be as much as 40 years in general populations of women [34, 35]. Results from our study are consistent with a long induction period, as women who smoked 20 years or longer had a more than 50 % increased risk of developing Luminal breast cancers. Further, among former smokers smoking cessation within 5–10 years of case/control selection was associated with increased Luminal breast cancer risk, whereas quitting within 5 or ≥11 years was not associated with risk. Previous studies have also demonstrated an association between smoking cessation 5–10 years prior to interview date and increased risk of ER+ or any breast cancer [6, 18]. These results suggest that the anti-estrogenic properties of cigarette smoke could suppress breast cancer development during periods of active smoking,

which may otherwise have developed via estrogenic pathways. Future studies of smoking and subtype-specific breast cancer risk would benefit by critically evaluating smoking exposures among pre- and postmenopausal women, as levels of endogenous estrogens may interact with anti-estrogenic properties of cigarette smoke. Indeed, a number of studies have demonstrated differential effects of smoking among pre- and postmenopausal women for overall breast cancer risk, thereby suggesting biological interactions between smoking and endogenous estrogens [8, 9].

In general, both black and white women with smoking histories had increased risk of Luminal type breast cancers in CBCS. However, the strength of the associations between current smoking or long smoking duration and breast cancer risk was greater among black women; there was no pattern of elevated odds ratios among white women. We interpret these results cautiously as prior studies have reported positive associations between smoking and breast cancer risk in populations of black and white women [6, 9]. However, the differing magnitudes of the effect estimates observed in our study may reflect differences in unmeasured co-exposures or genetic variants. Several studies have investigated racial differences for smoking interaction with polymorphisms of the cytochrome P-450 enzymes and DNA repair genes, which act to neutralize the effects of DNA damage from carcinogens in cigarette smoke. These studies identified variants of CYP1A1 and several nucleotide excision repair genes that were associated with higher risks of breast cancer among black smokers when compared with white smokers [36, 37]. There is also evidence to suggest that smoking may be associated with differential risks of other carcinomas, according to race or ethnicity. In a study of smoking and lung cancer risk, African American and Native American smokers were more likely to develop lung cancer when compared with Japanese Americans, Latino Americans, and White Americans [38]. Similarly, researchers have observed higher associations between smoking and head and neck cancers among African Americans when compared with White Americans, after controlling for other traditional risk factors [39]. Thus, in addition to subtype-specific investigations, future studies of smoking and breast cancer risk may benefit by examining associations by race.

The results presented in this paper should be interpreted in consideration of our study's limitations and strengths. Notably, case–control study designs may be susceptible to recall bias, with cases showing differential accuracy in recalling smoking histories. However, the use of self-reported smoking measures is shown to be a reliable method for active smoking assessment in the general US population [40]. In addition, urinary cotinine concentrations have been used to demonstrate the validity of self-reported smoking status (i.e., current, former, or never) [41]. The 55 % response rate among controls may generate concerns of selections bias since it is believed that non-smokers may be more likely to participate as controls in epidemiology studies [42]. However, 20 % of CBCS controls reported that they were current smokers, which is comparable to the 1995 estimate of 22 % for smoking prevalence among women in North Carolina [43]. Finally, we note that our race, subtype-specific, and other stratified analyses are limited by small sample size. Although several studies have reported associations between smoking before first pregnancy and breast cancer risk, our small sample sizes may have limited our ability to observe overall and subtype-specific associations.

Our investigation of smoking and breast cancer risk had a number of strengths. To our knowledge, this is the first study to examine the association between smoking and etiologic subtypes of breast cancer—the Luminal and Basal-like breast cancer types—by staining for proteins specific to Basal-like breast cancers [24]. Prior studies have examined smoking and subtype-specific breast cancer risk in relation to IHC staining of one or more of three clinical markers, which include the estrogen receptor, progesterone receptor and human epidermal growth factor receptor-2 (HER2). The additional IHC staining for human epidermal growth factor receptor-1 (HER1) and cytokeratin 5/6 (CK5/6) allowed us greater classification accuracy in identifying Basal-like breast cancers. Further, the CBCS oversampled young and black women, which allowed us to examine potential race differences for smoking and type specific breast cancer risk.

In conclusion, results from our study demonstrate associations between smoking and Luminal breast cancer risk, particularly among black women and women with long smoking histories. In addition, current smokers and former smokers with long smoking histories may be at higher risk of developing Luminal breast cancer. By examining active smoking exposure in relation to etiologic types of breast cancer, future investigations may clarify the unsettled question of whether smoking is associated with increased breast cancer risk.

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Table 1

CBCS I and II

Characteristics	Cases		Controls		X^2
	n = (1808)		*n = (1564)*		*p value*
	n	*%*	*n*	*%*	
Race					
Black	788	43.6	718	45.9	0.18
White	1,020	56.4	846	54.1	
Age					
< 50	976	54.0	787	50.3	0.03
≥50	832	46.0	777	49.7	
Postmenopause					
Yes	935	51.7	846	54.1	0.17
No	873	48.2	718	45.9	
Missing	0		0		
First-degree family history of breast cancer					
Yes	292	16.7	183	12.1	0.00
No	1,461	83.3	1328	87.9	
Missing	55		53		
Alcohol use					
Recent	1,004	55.6	863	55.2	0.70
Former	238	13.2	194	12.4	
Never	565	31.3	506	32.4	
Missing	1		1		
Oral contraceptive use (years)					
> 10	228	12.7	169	10.9	0.14
5–10	411	22.8	323	20.8	
< 5	538	29.9	489	31.5	
Never	625	34.7	572	36.8	
Missing	6		11		
Parity					

Characteristics	Cases		Controls		X^2
	n = (1808)		*n = (1564)*		*p value*
	n	*%*	*n*	*%*	
≥3	659	36.4	614	39.3	0.01
2	558	30.9	495	31.6	
1	316	17.5	281	18.0	
0	275	15.2	174	11.1	
Age at first birth					
≥25	478	26.4	401	25.6	0.00
< 25	1,055	58.4	989	63.2	
Never	275	15.2	174	11.1	
Age at first breastfeeding[a]					
≥25	290	19.0	272	19.6	0.25
< 25	341	22.3	341	24.6	
Never	899	58.8	776	55.9	
Missing	3		1		
Age at menarche					
< 12	1,401	77.5	1,250	79.9	0.09
≥12	407	22.5	314	20.1	
Body mass index (kg/m²)					
≥30	626	35.4	590	38.6	0.01
25–29	515	29.1	472	30.9	
< 25	627	35.5	466	30.5	
Missing	40		36		

Characteristics among breast cancer cases and controls

[a] Among parous women

Table 2

CBCS I and II

Characteristics	Cases		Controls		OR	95 % CI	
	n = (1808)		*n* = (1564)				
	n	%	*n*	%			
Smoking history							
Never	942	52.1	840	53.7	1.00		
Ever	866	47.9	724	46.3	1.07	0.92	1.25
Missing	0		0				
Smoking status							
Never	942	52.1	840	53.7	1.00		
Former	468	25.9	398	25.4	1.11	0.93	1.33
Current	398	22.0	326	20.8	1.02	0.84	1.24
Missing	0		0				
Smoking dose (packs per day)							
Never	942	52.2	840	53.8	1.00		
< 1/2	291	16.1	265	16.9	1.06	0.86	1.30
1/2–1	321	17.8	244	15.6	1.12	0.91	1.38
> 1	249	13.8	212	13.6	1.03	0.82	1.29
Missing	5		3				
Duration (years)							
Never	942	52.2	840	53.8	1.00		
≤10	235	13.0	219	14.0	0.86	0.69	1.08
11–20	206	11.4	186	11.9	0.95	0.75	1.21
> 20	420	23.3	315	20.2	1.33	1.09	1.61
Missing	5		4				
Duration among current (years)							
Never	942	70.40	840	72.16	1.00		
≤10	48	3.59	36	3.09	0.75	0.46	1.23
11–20	82	6.13	80	6.87	0.69	0.48	0.99
> 20	266	19.88	208	17.87	1.22	0.97	1.53

Characteristics	Cases		Controls		OR	95 % CI	
	n = (1808)		*n* = (1564)				
	n	%	*n*	%			
Missing	2		2				
Duration among former (years)							
Never	942	66.95	840	67.96	1.00		
≤10	187	13.29	183	14.81	0.89	0.70	1.14
11–20	124	8.81	106	8.58	1.15	0.85	1.54
> 20	154	10.95	107	8.66	1.54	1.15	2.07
Missing	3		2				
Years since quitting (former)							
Never	942	67.14	840	67.91	1.00		
< 5	82	5.84	66	5.34	1.02	0.71	1.48
5–10	120	8.55	78	6.31	1.39	1.01	1.93
11–20	136	9.69	126	10.19	1.04	0.79	1.37
> 20	123	8.77	127	10.27	1.01	0.76	1.35
Missing	7		1				
Age at initiation (years)							
Never	942	52.10	840	53.71	1.00		
≤15	137	7.58	112	7.16	0.89	0.66	1.19
16–20	477	26.38	410	26.21	1.07	0.89	1.28
> 20	252	13.94	202	12.92	1.19	0.95	1.49
Missing							
Initiation of smoking relative to menarche & first full-term pregnancy							
Never	801	52.25	735	52.88	1.00		
≤Menarche	48	3.13	43	3.09	0.82	0.51	1.31
After menarche, 11+ years before FFTP	80	5.22	63	4.53	1.03	0.70	1.52
After menarche, <11 years before FFTP	604	39.40	549	39.50	1.02	0.86	1.21

Odds ratios for smoking and breast cancer risk

ORs adjusted for age, race, family history, alcohol use, menopausal status, oral contraceptive use, parity, age at first birth, age at first breastfeeding, age at menarche, body mass index, and offsets

Table 3

CBCS I and II

Characteristics	Controls		Luminal					Basal-like					LRT
	Controls		Cases		OR	95 % CI		Cases		OR	95 % CI		*p* value
	n	%	*n*	%				*n*	%				
Smoking history													
Never	840	53.7	369	50.1	1.00			114	55.6	1.00			0.12
Ever	724	46.3	368	49.9	1.12	0.92	1.36	91	44.4	0.96	0.69	1.32	
Missing	0		0					0					
Smoking status													
Never	840	53.7	369	50.1	1.00			114	55.6	1.00			0.17
Former	398	25.4	200	27.1	1.11	0.88	1.40	50	24.4	1.09	0.74	1.61	
Current	326	20.8	168	22.8	1.10	0.86	1.41	41	20	0.82	0.54	1.24	
Missing	0		0					0					
Smoking dose (packs per day)													
Never	840	53.8	369	50.1	1.00			114	55.6	1.00			0.02
< 1/2	265	16.9	121	16.4	1.10	0.84	1.44	35	17.1	1.05	0.68	1.63	
1/2 to 1	244	15.6	132	17.9	1.13	0.86	1.47	43	21.0	1.22	0.80	1.84	
> 1	212	13.6	114	15.5	1.08	0.81	1.44	13	6.3	0.47	0.25	0.89	
Missing	3		1					0					
Duration (years)													
Never	840	53.8	369	50.2	1.00			114	55.6	1.00			0.00
≤10	219	14.0	89	12.1	0.79	0.58	1.06	31	15.1	0.91	0.58	1.44	
11–20	186	11.9	79	10.7	0.89	0.65	1.23	28	13.7	1.01	0.62	1.64	
> 20	315	20.2	198	26.9	1.51	1.19	1.93	32	15.6	0.90	0.57	1.43	
Missing	4		2					0					
Duration among current (years)													
Never	840	72.2	369	69.0	1.00			114	73.5	1.00			0.06
≤10	36	3.1	18	3.4	0.68	0.35	1.32	5	3.2	0.52	0.19	1.42	
11–20	80	6.9	26	4.9	0.56	0.34	0.94	13	8.4	0.72	0.36	1.45	
> 20	208	17.9	122	22.8	1.41	1.06	1.88	23	14.8	0.94	0.56	1.59	

Characteristics	Controls		Luminal					Basal-like					LRT
	Controls		Cases		OR	95 % CI		Cases		OR	95 % CI		*p* value
	n	%	*n*	%				*n*	%				
Missing	2		2					2					
Duration among former (years)													
Never	840	68.0	369	64.9	1.00			114	69.5	1.00			0.14
≤10	183	14.8	71	12.5	0.80	0.58	1.11	26	15.9	1.06	0.65	1.73	
11–20	106	8.6	53	9.3	1.14	0.78	1.67	15	9.1	1.27	0.69	2.34	
> 20	107	8.7	76	13.4	1.69	1.18	2.43	9	5.5	0.78	0.34	1.80	
Missing	2		0					0					
Years since quitting (former)													
Never	840	67.9	369	65.1	1.00			114	69.5	1.00			0.91
< 5	66	5.3	32	5.6	0.89	0.55	1.44	9	5.5	0.87	0.39	1.93	
5–10	78	6.3	48	8.5	1.33	0.88	2.01	11	6.7	1.25	0.62	2.51	
11–20	126	10.2	62	10.9	1.08	0.76	1.54	20	12.2	1.25	0.72	2.17	
> 20	127	10.3	56	9.9	1.05	0.73	1.51	10	6.1	0.85	0.41	1.79	
Missing	1		2					0					
Age at initiation (years)													
Never	840	53.7	369	50.1	1.00			114	55.6	1.00			0.32
≤15	112	7.2	51	6.9	0.82	0.56	1.21	15	7.3	0.89	0.48	1.66	
16–20	410	26.2	213	28.9	1.15	0.91	1.44	49	23.9	0.91	0.62	1.34	
> 20	202	12.9	104	14.1	1.18	0.88	1.57	27	13.2	1.07	0.66	1.75	
Missing	0		0						0				
Initiation of smoking relative to menarche and first full-term pregnancy													
Never	735	52.88	309	50.0	1.00			101	55.8	1.00			0.25
≤Menarche	43	3.09	17	2.8	0.83	0.46	1.53		7	3.9	1.18	0.49	2.85
After menarche, 11+ years before FFTP	63	4.53	34	5.5	1.05	0.64	1.73		6	3.3	0.78	0.31	1.98
After menarche, <11 years before FFTP	549	39.50	258	41.7	1.05	0.84	1.32	67	37.0	0.84	0.58	1.22	

Odds ratios for smoking and breast cancer among cases and controls

ORs adjusted for age, race, family history, alcohol use, menopausal status, oral contraceptive use, parity, age at first birth, age at first breastfeeding, age at menarche, body mass index, and offsets

LRT likelihood ratio test

Table 4

CBCS I and II

Characteristics	Controls		Luminal					Basal-like					LRT
	Controls		Cases		OR	95 % CI		Cases		OR	95 % CI		*p* value
	n	%	*n*	%				*n*	%				
Black study participants: odds ratios for smoking and Luminal or Basal-like breast cancer risk													
Smoking history													
Never	425	59.2	151	52.8	1.00			65	55.1	1.00			0.42
Ever	293	40.8	135	47.2	1.40	1.03	1.92	53	44.9	1.19	0.77	1.83	
Missing	0												
Smoking status													
Never	425	59.2	151	52.8	1.00			65	55.1	1.00			0.02
Former	146	20.3	62	21.7	1.20	0.81	1.78	32	27.1	1.71	1.02	2.86	
Current	147	20.5	73	25.5	1.53	1.04	2.26	21	17.8	0.77	0.43	1.39	
Missing	0		0					0					
Smoking dose (packs per day)													
Never	425	59.3	151	52.8	1.00			65	55.1	1.00			0.41
< 1/2	137	19.1	57	19.9	1.35	0.90	2.00	23	19.5	1.21	0.69	2.10	
1/2–1	105	14.6	56	19.6	1.46	0.96	2.22	25	21.2	1.36	0.78	2.38	
> 1	50	7.0	22	7.7	1.22	0.68	2.20	5	4.2	0.66	0.24	1.78	
Missing	1		0					0					
Duration (years)													
Never	425	59.4	151	52.8	1.00			65	55.1	1.00			0.06
≤10	92	12.8	33	12.6	0.97	0.60	1.57	17	14.4	1.09	0.59	2.02	
11–20	82	11.5	27	9.3	1.01	0.60	1.71	18	15.3	1.31	0.69	2.47	
> 20	117	16.3	75	25.2	2.06	1.38	3.06	18	15.3	1.13	0.61	2.10	
Missing	2		0					0					
White study participants: odds ratios for smoking and Luminal or Basal-like breast cancer risk													
Smoking history													
Never	415	49.1	218	48.3	1.00			49	56.3	1.00			0.30
Ever	431	50.9	233	51.7	0.99	0.77	1.28	38	43.7	0.76	0.46	1.25	

Characteristics	Controls		Luminal					Basal-like					LRT
	Controls		Cases		OR	95 % CI		Cases		OR	95 % CI		*p* value
	n	%	*n*	%				*n*	%				
Missing	0		0					0					
Smoking status													
Never	415	49.1	218	48.3	1.00			49	56.3	1.00			0.31
Former	252	29.8	138	30.6	1.05	0.78	1.40	18	20.7	0.68	0.36	1.27	
Current	179	21.2	95	21.1	0.91	0.65	1.26	20	23.0	0.86	0.47	1.60	
Missing	0		0					0					
Smoking dose (packs per day)													
Never	415	49.2	218	48.4	1.00			49	56.3	1.00			0.10
< 1/2	128	15.2	64	14.2	0.95	0.66	1.37	12	13.8	1.01	0.48	2.10	
1/2–1	139	16.5	76	16.9	0.97	0.69	1.38	18	20.7	1.05	0.55	1.98	
> 1	162	19.2	92	20.4	1.03	0.73	1.43	8	9.2	0.38	0.16	0.90	
Missing	2		1					0					
Duration (years)													
Never	415	49.2	218	49.2	1.00			49	56.3	1.00			0.14
≤10	127	15.0	56	11.6	0.70	0.47	1.02	14	16.1	0.78	0.39	1.56	
11–20	104	12.3	52	11.4	0.84	0.56	1.25	10	11.5	0.66	0.30	1.44	
> 20	198	23.5	123	27.8	1.31	0.96	1.79	14	16.1	0.79	0.39	1.59	
Missing	2		2					0					

ORs adjusted for age, family history, alcohol use, menopausal status, oral contraceptive use, parity, age at first birth, age at first breastfeeding, age at menarche, body mass index, and offsets

LRT likelihood ratio test