Published in final edited form as:
Cancer Causes Control. 2013 December ; 24(12): . doi:10.1007/s10552-013-0298-6.

A prospective study of smoking and breast cancer risk among African American women

Lynn Rosenberg[1], **Deborah A. Boggs**[1], **Traci N. Bethea**[1], **Lauren A. Wise**[1], **Lucile L. Adams-Campbell**[2], and **Julie R. Palmer**[1]

Deborah A. Boggs: dboggs@bu.edu; Traci N. Bethea: trb@bu.edu; Lauren A. Wise: lwise@bu.edu; Lucile L. Adams-Campbell: lla9@georgetown.edu; Julie R. Palmer: jpalmer@bu.edu

[1]Slone Epidemiology Center at Boston University, Boston, MA

[2]Lombardi Comprehensive Cancer Center, Georgetown University, Washington, DC

Abstract

Purpose—Active smoking and passive smoking have been associated with increased risk of breast cancer. The purpose of the present study was to prospectively assess associations of smoking with breast cancer and identify subgroups at higher risk among African American women.

Methods—Based on 1,377 incident cases identified during 14 years of follow-up in the Black Women's Health Study, we assessed active and passive smoking in relation to breast cancer incidence by menopausal status, estrogen receptor status, and other factors. Incidence rate ratios (IRR) and 95% confidence intervals (CI) for categories of smoking relative to no active or passive smoking were calculated from Cox proportional hazards models, controlling for breast cancer risk factors.

Results—Active smoking was associated with increased risk of premenopausal breast cancer. The IRR was 1.21 (95% CI 0.90–1.62) for premenopausal breast cancer overall, and 1.70 (95% CI 1.05–2.75) for premenopausal breast cancer associated with beginning smoking before age 18 together with accumulation of ≥ 20 pack years. The positive association with premenopausal breast cancer was most apparent for estrogen receptor positive cancer. Passive smoking was also associated with increased risk of premenopausal breast cancer (IRR=1.42, 95% CI 1.09–1.85), based on information on passive smoking at home and work. Neither active nor passive smoking was associated with increased risk of postmenopausal breast cancer.

Conclusion—These results strengthen the evidence that both active and passive smoking increase the incidence of premenopausal breast cancer.

Keywords

African American; female; breast cancer; smoking

Introduction

Carcinogens are present in the smoke inhaled by cigarette smokers (active smoking) and from the exhalation of the smoker and the lit end of the cigarette (passive smoking)[1–3]. Tobacco smoke contains fat-soluble mutagenic compounds that have been detected in

Corresponding author: Lynn Rosenberg, Sc.D., 1010 Commonwealth Avenue, Boston, MA 02215; telephone 617 734-6006; fax 617 738-5119; lrosenbe@bu.edu.

Competing interests: The authors declare that they have no competing interests.

human breast fluid[4] and can induce mammary tumors in animals[3], and higher levels of DNA adducts and mutations in the p-53 gene have been found in the breast tissue of smokers[1, 5].

Numerous epidemiologic studies, largely of white women, have assessed smoking in relation to breast cancer risk[6]. Many of the earlier studies were null[1, 7, 8]. However, evidence has accumulated that active smoking may increase risk [9–13], and follow-up studies published in the last decade have consistently found higher breast cancer risk among smokers with substantial exposure [14–21]. Risk may be greater for smoking at a young ages [11] or before the first birth[22]; these exposures are of special interest because rapidly dividing cells during breast tissue development may be more susceptible to carcinogens[23, 24]. The possibility of a differential effect of smoking by estrogen receptor status of the tumor is also of interest because some risk factors for estrogen receptor positive (ER+) and negative (ER−) breast cancer differ[25, 26], and constituents of smoke can bind to estrogen receptors[27]. Results of the few studies of smoking and breast cancer by receptor status have been conflicting[18, 21, 28–30].

Passive smoking has been associated in some studies with increased risk of premenopausal [9, 10, 28, 31–34] and postmenopausal breast cancer[29, 35], but other studies have found no increase for premenopausal[36], postmenopausal [36], or overall breast cancer risk [37, 38]. Some reviews find the evidence for a link with premenopausal breast cancer to be convincing[9, 11] but others are skeptical[10, 13].

Previous findings on the association of smoking with breast cancer among African American women are limited[39], and there are no published prospective data on the association. With data from the Black Women's Health Study (BWHS), we prospectively assessed active and passive smoking in relation to the incidence of invasive breast cancer overall and according to menopausal status, hormone receptor status, and other factors among African American women.

Methods

The Black Women's Health Study

The BWHS began in 1995 when 59,000 self-described black women ages 21–69 years from across the mainland United States enrolled by completing mailed health questionnaires. Participants have been followed biennially through mailed and web questionnaires[40]. Notifications of deaths are obtained from family members, the U.S. postal service, and the National Death Index. Follow-up of the baseline cohort was 80% after seven completed follow-up cycles. Informed consent is indicated by the completion of the questionnaires. The Institutional Review Board of Boston University Medical Center approved the research.

Data collection

At baseline in 1995, participants reported active smoking (having smoked ≥ 1 cigarette per day for at least a year currently or in the past); age started smoking regularly (≤14, 15, 16, 17, 18, 19, 20, ≥ 21 years); number of cigarettes smoked per day (<5, 5–14, 15–24, 25–34, 35–44, ≥ 45); and years of smoking (<10, 10–14, 15–19, 20–24, 25–29, ≥ 30). The number of cigarettes currently smoked (none, <5, 5–14, 15–24, 25–34, ≥ 35 per day) was updated on follow-up questionnaires. The 1997 questionnaire asked about exposure to a smoker at least an hour a day for at least 12 consecutive months at home at ages 0–10, 11–20, and 21–30 and at work at ages 21–30; we defined passive smoking as a positive response to any of these questions. Pack years of active smoking was calculated as the product of the years of smoking (midpoint of category) and the number of cigarettes smoked (midpoint of category).

Information was collected at baseline on height, weight, years of education, family history of breast cancer, number of births, age at first birth, oral contraceptive use, menopausal female hormone use, vigorous exercise, alcoholic beverage consumption, menopausal status, and age at menopause. All except height were updated on follow-up questionnaires.

Breast cancer cases

Incident cases were identified through self-report on follow-up questionnaires through 2009. More than 99% of cases for which pathology reports from hospitals and cancer registries were obtained have been confirmed as breast cancer. The present report is based on 1,377 breast cancer cases, of which 1,097 were confirmed as invasive breast cancer by pathology data. In view of the high confirmation rate among cases for which pathology data were available, we also included 280 cases for which records were not yet obtained. Hormone receptor status was available for 854 cases; breast cancer risk factors did not differ between cases with known and unknown receptor status [41, 42].

Analysis

After exclusion of 1,462 women who reported having cancer at baseline and 5,114 women who did not complete the active smoking questions at baseline or the passive smoking questions in 1997, there were 52,425 women remaining, who were followed through 2009.

We used Cox proportional hazards regression to estimate incidence rate ratios (IRRs) and 95% confidence intervals (CI) for the association of smoking with breast cancer relative to never smoked actively or passively (SAS version 9.1.3). Women contributed person-time from baseline until breast cancer diagnosis, death, or loss to follow-up, whichever came first. Women who developed in-situ breast cancer were censored at that point. The smoking variables and time-varying covariates were updated each questionnaire cycle. For example, a current smoker contributed person years to the current smoking category; if she reported having stopped smoking, her person-years starting with that questionnaire were contributed to the former smoking category. The Cox models were jointly stratified by age in 1-year intervals and questionnaire cycle and included terms for body mass index (BMI, kg/m^2) (<25, 25–29, ≥ 30), years of education (≤12, 13–15, ≥ 16), family history of breast cancer (yes, no), age at menarche (≤11, 12–13, ≥ 14), parity (0, 1, 2, ≥ 3), age at first birth (<20, 20–24, ≥ 25), years of oral contraceptive use (never used, <5, ≥ 5), hours per week of vigorous exercise (none, <5, ≥ 5), alcoholic beverage consumption (never drank, past drinker, current consumption of 1–6 drinks/week, current consumption of ≥ 7 drinks/week), menopausal status (premenopausal, postmenopausal, uncertain), age at menopause (<45, 45–49, ≥ 50), and years of menopausal female hormone use (never used, <5, ≥ 5). Women with a hysterectomy without removal of both ovaries were classified as premenopausal if their current age was <43 (10^{th} percentile of age at natural menopause in the BWHS), postmenopausal if their age was ≥ 57 (90^{th} percentile of age at natural menopause in the cohort), and as having unknown menopausal status for ages 43–56 years. Tests for interaction were performed using the likelihood ratio test comparing models with and without cross-product terms between the covariates of interest.

Results

As shown in table 1, at baseline women with greater pack years of active smoking were more likely to be older, obese (BMI ≥ 30), have lower educational attainment, higher parity, younger age at first birth, less participation in strenuous exercise, and greater alcohol consumption than women who smoked less or never smoked actively or passively. The characteristics of passive smokers were generally intermediate between those of active smokers and women who never smoked actively or passively. Family history of breast

cancer, oral contraceptive use, menopausal female hormone use, and menopausal status did not vary appreciably according to active or passive smoking.

The IRRs for ever active smoking and passive smoking, relative to never active or passive smoking, were 1.08 (95% CI 0.89–1.31) and 1.18 (95% CI 0.98–1.42), respectively (table 2). The IRR for ever active smoking was 1.21 (95% CI 0.90–1.62) for premenopausal breast cancer and 0.92 (95% CI 0.68–1.24) for postmenopausal breast cancer. Passive smoking was associated with increased risk of premenopausal breast cancer (IRR=1.42, 95% CI 1.09–1.85), and the IRR for postmenopausal breast cancer was less than 1.0. The IRR for premenopausal breast cancer for the highest exposure to passive smoking (at each of ages 0–10 and 11–20 at home and at ages 21–30 at home and work) was 1.70, 95% CI 1.10–2.63, based on 31 exposed cases.

As shown in table 3, the IRR for breast cancer overall for the highest category of pack years of active smoking considered, ≥ 20, was 1.20 (95% CI 0.95–1.52). The increase was accounted for by a positive association with premenopausal breast cancer (IRR =1.33, 95% CI 0.86–2.05); the corresponding estimate for postmenopausal breast cancer was less than 1.0. The p-value for interaction by menopausal status was 0.34. The increase in risk of premenopausal breast cancer was greater if smoking was initiated before age 18: the IRR for smoking before age 18 together with ≥ 20 pack years was 1.70 (95% CI 1.05–2.75). There were no increases in risk for smoking initiated at age 18 or older. Neither smoking before age 18 nor smoking that began later was associated with increased risk of postmenopausal breast cancer.

Results of analyses according to whether smoking occurred before or after the first birth are given in table 4. The IRRs for premenopausal breast cancer for smoking for <5 years before the first term birth, ≥ 5 years before the first birth, and after the first birth only were all increased: 1.47 (95% CI 0.92–2.33), 1.54 (95% CI 1.03–2.30), and 1.33 (95% CI 0.81–2.19), respectively. The corresponding IRRs for postmenopausal breast cancer were below 1.0. Among women who accumulated ≥ 20 pack-years, the IRR for premenopausal breast cancer was 1.64 (95% CI 0.78–3.46) for <5 years of smoking before the first birth and 2.01 (95% CI 1.10–3.65) for ≥ 5 years of smoking after the first birth.

In analyses of nulliparous women (n=277), the IRR for ≥ 20 pack years of smoking associated with breast cancer overall was 1.09 (95% CI 0.65–1.80), based on 30 exposed cases; the corresponding estimate for premenopausal breast cancer was 0.94 (95% CI 0.37–2.36), based on 6 exposed cases.

Table 5 shows pack years of active smoking and smoking before age 18 in relation to premenopausal breast cancer in categories of BMI, alcohol consumption, and estrogen receptor status. IRRs were generally increased for ≥ 20 pack years and even more so if smoking began before age 18. The IRR associated with ≥ 20 pack years of smoking was 2.22 (95% CI 1.09–4.54) among women with BMI <25 and 1.01 (95% CI 0.58–1.77) among women with BMI ≥ 25 (p interaction = 0.12). The association with ≥ 20 pack years was similar among women who ever drank alcohol (IRR= 1.40, 95% CI 0.76–2.58) and those who never drank (IRR=1.41, 95% CI 0.70–2.83). The IRR for ER+ breast cancer associated with ≥ 20 pack years of smoking was 1.85 (95% CI 0.96–3.57), and it was 2.58 (95% CI 1.26–5.29) if the smoking began before age 18; the IRRs for ER− cancer were less than 1.00. To test the differences in the IRRs by receptor status, we confined a Cox regression model to ER+ and ER− cases; none of the IRRs differed from 1.0 at the 0.05 level of significance.

We also assessed passive smoking in relation to premenopausal breast cancer within strata of the categories shown in table 5. There were no notable differences between strata.

Specifically, for the categories BMI <25, BMI ≥ 25, alcohol drinker, never drinker, ER+ cancer, and ER− cancer, the IRRs were 1.43 (95% CI 0.91–2.27), 1.37 (95% C 0.99–1.89), 1.61 (95% CI 1.02–2.55), 1.31 (95% CI 0.94–1.81), 1.27 (95% CI 0.82–1.96) and 1.52 (0.92–2.52), respectively

There were no increases in risk of postmenopausal breast cancer associated with ≥ 20 pack years of smoking, smoking initiation before age 18, or passive smoking, in the categories of factors shown in table 5 (data not shown).

Discussion

In this follow-up study, active smoking was associated with increased risk of premenopausal breast cancer, in agreement with many previous studies. There was no increase in postmenopausal cancer risk, but the difference in risk by menopausal status was not statistically significant. In studies conducted before 2009, risk estimates for an association with smoking were generally higher for premenopausal than for postmenopausal breast cancer [11, 12]. In two recent large case-control studies, active smoking was associated with premenopausal breast cancer but not with postmenopausal breast cancer[28, 43], and in a third it is was associated more strongly with premenopausal cancer[44]. In recent follow-up studies, smoking has been associated with increased risk of both premenopausal[14–16, 18, 45] and postmenopausal breast cancer[14, 15, 21]. In the largest study to date, based on data from the Nurses' Health Study, smoking after menopause was not associated with increased risk but smoking before menopause was associated with increased risk of both premenopausal and postmenopausal cancer[36]. Differences in the association of smoking with breast cancer by menopausal status may be explained by mechanisms that have opposing effects: carcinogens from cigarette smoke increase risk, but smoking also reduces estrogen levels, which would lower risk [46]. The reduction of estrogen levels by smoking might be most relevant when levels have declined, as among postmenopausal women, and could contribute to the absence of a positive association of smoking with postmenopausal breast cancer in some studies.

We found that the positive association of active smoking with premenopausal breast cancer was present for ER+ cancer and not for ER− cancer. Some studies have found stronger associations with ER+ cancer[18, 21, 28, 29] and a small study found a stronger association with ER− cancer[30] but, as in the present study, the differences have generally not been statistically significant. A follow-up study of the Women's Health Initiative cohorts found ≥ 40 pack years of smoking to be associated with increased risk of ER+ cancer but not of triple negative breast cancer, a subgroup of ER− cancer; results on ER− cancer as a whole were not presented [47]. A stronger association with ER+ cancer could involve the binding of tobacco carcinogens to estrogen receptors [27].

Smoking initiated at a young age has been consistently associated with a greater increase in risk of breast cancer than smoking begun later [2, 15, 18, 48]. However, early starters tend to smoke longer [15, 36] and many studies did not control duration or amount of smoking when assessing age started. In the present study, results from assessment of age started within categories of pack years suggest that early initiation is an important contributor to increased risk of premenopausal breast cancer beyond that of duration and amount smoked. In addition, the lack of an association of early smoking with increased risk unless there had also been appreciable pack years of smoking subsequently suggests that the association with early initiation is not simply a latency effect.

In the present study both active smoking that occurred before the first birth and active smoking that began after the first birth were associated with increased risk. Many studies

have suggested higher breast cancer risk for women who smoked before the first birth [14–16, 21, 29, 36, 48, 49], although two recent follow-up studies found no difference [22, 24]. In the Nurses' Health Study, after control in detail for the duration of smoking at other ages, smoking before the first birth was associated with greater risk than smoking after the first birth[19, 36].

We found that smoking was not associated with increased breast cancer risk among nulliparous women, in agreement with the Nurses' Health Study[19]. The null results among the relatively small numbers of nulliparous women may reflect lower statistical power. Alternatively, a greater risk among parous smokers could indicate that the mammary cell proliferation that occurs during or after pregnancy makes women more vulnerable to the effects of tobacco carcinogens [50, 51].

The increased risk of premenopausal breast cancer associated with smoking in the present study was apparent only among women with a BMI <25. In contrast, an association of active smoking with premenopausal breast cancer in a case-control study was stronger in obese women [28]. In the Women's Health Initiative follow-up study of postmenopausal women, active smoking was associated with increased breast cancer risk only among women with BMI < 30 [52]. Other evidence on the possibility that weight modifies an effect of smoking is sparse.

It has been suggested that alcohol consumption, which is a risk factor for breast cancer[53], could account for positive associations of smoking with breast cancer. The suggestion was based on the lack of association of ever smoking with breast cancer risk among nondrinkers in a combined analysis that included over 58,000 breast cancer cases[54]. However, substantial smoking rather than ever smoking has been most consistently associated with increased breast cancer risk[11]. In addition, most studies that have found associations with smoking controlled for alcohol consumption. In the present study, a positive association of smoking and breast cancer risk was present after control for the timing and amount of alcohol consumption, and there was also an association among never drinkers. Recent follow-up studies have also found increases in breast cancer risk for smokers who were nondrinkers [14, 15].

We found passive smoking to be associated with increased risk of premenopausal breast cancer, in agreement with some studies [9, 10, 28, 31–34], but other studies have been null [36–38]. Two recent follow-up studies reported positive associations with postmenopausal breast cancer[14, 29]. The passive smoking information in many studies, including our own, has been limited. We had data on passive smoking at several ages at home and work but not on the duration or intensity of exposure.

Previous results on smoking and breast cancer in African American women specifically are quite limited. The Carolina Breast Cancer Study assessed the association of smoking with breast cancer risk in a population-based case-control study of African American women (894 cases) and white women (1234 cases)[39]. Active and passive smoking were associated with increased risk of breast cancer among African American women; risk increased with increasing duration of smoking but was unrelated to the age started smoking. Smoking was not associated with breast cancer risk among white women. Results within strata of menopausal status, body size, or estrogen receptor status of the tumor were not presented.

Results from case-control studies have been less consistent than those from cohort studies, possibly reflecting reporting bias or selective enrollment according to smoking status in some studies. Prospective data collection in the present study obviates concern about reporting bias, and completeness of follow-up was satisfactory. The information on smoking was updated throughout follow-up, and we controlled for important potential confounding

variables. We used a reference category of never active or passive smoking because, if passive smoking increases risk of breast cancer, inclusion of passive smoking in the reference category will have diluted associations with active smoking[31, 44]. Analyses in subgroups were limited by small numbers.

Racial differences have been found in the association of smoking with risk of lung cancer. Specifically, in the Multiethnic Cohort Study, African American and Native Hawaiian smokers appeared more susceptible to developing lung cancer than whites, Japanese Americans, and Latinos[55]. This finding raises the possibility that the influence of smoking on breast cancer risk could differ by race. The present results on smoking and breast cancer, and those of the Carolina Breast Cancer Study specifically in African American women[39], are consistent with those of many previous studies in white women and do not support a difference by race. Confounding factors differ across populations. Among the African American women in the present study, active smoking was strongly positively associated with body mass index and early age at first birth. In contrast, among the white women in the Nurses' Health Study[36] and Nurses' Health Study II[18], smoking was inversely associated with body mass index and weakly associated with age at first birth. The fact that studies of different ethnic groups with varying patterns of confounding factors have found associations of prolonged smoking with increased breast cancer risk adds credibility that the associations are real.

Conclusion

The present results strengthen the evidence that active and passive smoking increase the risk of premenopausal cancer. Very large studies, or combined analyses, are needed to clearly determine when during the lifespan smoking is most hazardous in terms of breast cancer risk and which subgroups of women are most affected.

Acknowledgments

This work was supported by National Cancer Institute grant R01 CA058420. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Cancer Institute or the National Institutes of Health. Data on breast cancer pathology were obtained from several state cancer registries (AZ, CA, CO, CT, DE, DC, FL, GA, IL, IN, KY, LA, MD, MA, MI, NJ, NY, NC, OK, PA, SC, TN, TX, VA) and results reported do not necessarily represent their views. Dr. Rosenberg had full access to all the data and takes responsibility for the integrity of the data and the accuracy of the data analysis. The authors are grateful to the BWHS participants and staff.

References

1. Tobacco Smoke and Involuntary Smoking. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Vol. 83. International Agency for Research on Cancer; Lyon, France: IARC Press; 2004.
2. Johnson KC, et al. Active smoking and secondhand smoke increase breast cancer risk: the report of the Canadian Expert Panel on Tobacco Smoke and Breast Cancer Risk (2009). Tob Control. 2011; 20(1):e2. [PubMed: 21148114]
3. Hoffmann D, Hoffmann I, El-Bayoumy K. The less harmful cigarette: a controversial issue. a tribute to Ernst L. Wynder. Chem Res Toxicol. 2001; 14(7):767–90. [PubMed: 11453723]
4. Petrakis NL. Nipple aspirate fluid in epidemiologic studies of breast disease. Epidemiol Rev. 1993; 15(1):188–95. [PubMed: 8405203]
5. Conway K, et al. Prevalence and spectrum of p53 mutations associated with smoking in breast cancer. Cancer Res. 2002; 62(7):1987–95. [PubMed: 11929815]
6. Terry PD, Thun MJ, Rohan TE. Does tobacco smoke cause breast cancer? Womens Health (Lond Engl). 2011; 7(4):405–8. [PubMed: 21790331]

7. The Health Consequences of Smoking: A Report of the Surgeon General. U.S. Department of Health and Human Services; Atlanta, GA: 2004.
8. Palmer JR, Rosenberg L. Cigarette smoking and the risk of breast cancer. Epidemiol Rev. 1993; 15(1):145–56. [PubMed: 8405197]
9. Proposed Identification of Environmental Tobacco Smoke as a Toxic Air Contaminant. California Environmental Protection Agency; 2005.
10. The Health Consequences of Involuntary Exposure to Tobacco Smoke: A Report of the Surgeon General. U.S. Department of Health and Human Services; Atlanta, GA: 2006.
11. Collishaw, NE., et al. OTRU Special Report Series. Ontario Tobacco Research Unit; Toronto, Canada: 2009. Canadian Expert Panel on Tobacco Smoke and Breast Cancer Risk.
12. Terry PD, Rohan TE. Cigarette smoking and the risk of breast cancer in women: a review of the literature. Cancer Epidemiol Biomarkers Prev. 2002; 11(10 Pt 1):953–71. [PubMed: 12376493]
13. Secretan B, et al. A review of human carcinogens--Part E: tobacco, areca nut, alcohol, coal smoke, and salted fish. Lancet Oncol. 2009; 10(11):1033–4. [PubMed: 19891056]
14. Reynolds P, et al. Active smoking, household passive smoking, and breast cancer: evidence from the California Teachers Study. J Natl Cancer Inst. 2004; 96(1):29–37. [PubMed: 14709736]
15. Gram IT, et al. Breast cancer risk among women who start smoking as teenagers. Cancer Epidemiol Biomarkers Prev. 2005; 14(1):61–6. [PubMed: 15668477]
16. Olson JE, et al. Prepregnancy exposure to cigarette smoking and subsequent risk of postmenopausal breast cancer. Mayo Clin Proc. 2005; 80(11):1423–8. [PubMed: 16295021]
17. Cui Y, Miller AB, Rohan TE. Cigarette smoking and breast cancer risk: update of a prospective cohort study. Breast Cancer Res Treat. 2006; 100(3):293–9. [PubMed: 16773435]
18. Al-Delaimy WK, et al. A prospective study of smoking and risk of breast cancer in young adult women. Cancer Epidemiol Biomarkers Prev. 2004; 13(3):398–404. [PubMed: 15006915]
19. Egan KM, et al. Active and passive smoking in breast cancer: prospective results from the Nurses' Health Study. Epidemiology. 2002; 13(2):138–45. [PubMed: 11880753]
20. Terry PD, Miller AB, Rohan TE. Cigarette smoking and breast cancer risk: a long latency period? Int J Cancer. 2002; 100(6):723–8. [PubMed: 12209614]
21. Gaudet MM, et al. Active smoking and breast cancer risk: original cohort data and meta-analysis. J Natl Cancer Inst. 2013; 105(8):515–25. [PubMed: 23449445]
22. DeRoo LA, Cummings P, Mueller BA. Smoking before the first pregnancy and the risk of breast cancer: a meta-analysis. Am J Epidemiol. 2011; 174(4):390–402. [PubMed: 21719745]
23. Palmer JR, et al. Breast cancer and cigarette smoking: a hypothesis. Am J Epidemiol. 1991; 134(1):1–13. [PubMed: 1853854]
24. Lawlor DA, Ebrahim S, Smith GD. Smoking before the birth of a first child is not associated with increased risk of breast cancer: findings from the British Women's Heart and Health Cohort Study and a meta-analysis. Br J Cancer. 2004; 91(3):512–8. [PubMed: 15226777]
25. Althuis MD, et al. Etiology of hormone receptor-defined breast cancer: a systematic review of the literature. Cancer Epidemiol Biomarkers Prev. 2004; 13(10):1558–68. [PubMed: 15466970]
26. Ma H, et al. Hormone-related risk factors for breast cancer in women under age 50 years by estrogen and progesterone receptor status: results from a case-control and a case-case comparison. Breast Cancer Res. 2006; 8(4):R39. [PubMed: 16846528]
27. Habel LA, Stanford JL. Hormone receptors and breast cancer. Epidemiol Rev. 1993; 15(1):209–19. [PubMed: 8405205]
28. Lissowska J, et al. Tobacco smoking, NAT2 acetylation genotype and breast cancer risk. Int J Cancer. 2006; 119(8):1961–9. [PubMed: 16721725]
29. Luo J, et al. Association of active and passive smoking with risk of breast cancer among postmenopausal women: a prospective cohort study. BMJ. 2011; 342:d1016. [PubMed: 21363864]
30. Manjer J, et al. Smoking associated with hormone receptor negative breast cancer. Int J Cancer. 2001; 91(4):580–4. [PubMed: 11251985]
31. Johnson KC. Accumulating evidence on passive and active smoking and breast cancer risk. Int J Cancer. 2005; 117(4):619–28. [PubMed: 15929073]

32. Lissowska J, Brinton LA, Garcia-Closas M. Re: more data regarding the effects of passive smoking on breast cancer risk among younger women. Int J Cancer. 2007; 120(11):2517–8. [PubMed: 17290385]
33. Anderson LN, et al. Passive cigarette smoke exposure during various periods of life, genetic variants, and breast cancer risk among never smokers. Am J Epidemiol. 2012; 175(4):289–301. [PubMed: 22247046]
34. Kropp S, Chang-Claude J. Active and passive smoking and risk of breast cancer by age 50 years among German women. Am J Epidemiol. 2002; 156(7):616–26. [PubMed: 12244030]
35. Reynolds P, et al. Passive smoking and risk of breast cancer in the California teachers study. Cancer Epidemiol Biomarkers Prev. 2009; 18(12):3389–98. [PubMed: 19959687]
36. Xue F, et al. Cigarette smoking and the incidence of breast cancer. Arch Intern Med. 2011; 171(2): 125–33. [PubMed: 21263102]
37. Chuang SC, et al. Exposure to environmental tobacco smoke in childhood and incidence of cancer in adulthood in never smokers in the European Prospective Investigation into Cancer and Nutrition. Cancer Causes Control. 2011; 22(3):487–94. [PubMed: 21279734]
38. Pirie K, et al. Passive smoking and breast cancer in never smokers: prospective study and meta-analysis. Int J Epidemiol. 2008; 37(5):1069–79. [PubMed: 18544575]
39. Mechanic LE, et al. Polymorphisms in nucleotide excision repair genes, smoking and breast cancer in African Americans and whites: a population-based case-control study. Carcinogenesis. 2006; 27(7):1377–85. [PubMed: 16399771]
40. Russell CW, et al. Use of a web-based questionnaire in the Black Women's Health Study. Am J Epidemiol. 2010; 172(11):1286–91. [PubMed: 20937635]
41. Palmer JR, et al. Parity and lactation in relation to estrogen receptor negative breast cancer in African American women. Cancer Epidemiol Biomarkers Prev. 2011; 20(9):1883–91. [PubMed: 21846820]
42. Rosenberg L, et al. Oral contraceptive use and estrogen/progesterone receptor-negative breast cancer among African American women. Cancer Epidemiol Biomarkers Prev. 2010; 19(8):2073–9. [PubMed: 20647407]
43. Band PR, et al. Carcinogenic and endocrine disrupting effects of cigarette smoke and risk of breast cancer. Lancet. 2002; 360(9339):1044–9. [PubMed: 12383984]
44. Johnson KC, Hu J, Mao Y. Passive and active smoking and breast cancer risk in Canada, 1994–97. Cancer Causes Control. 2000; 11(3):211–21. [PubMed: 10782655]
45. Hanaoka T, et al. Active and passive smoking and breast cancer risk in middle-aged Japanese women. Int J Cancer. 2005; 114(2):317–22. [PubMed: 15540214]
46. Chen C, et al. Effect of environmental tobacco smoke on levels of urinary hormone markers. Environ Health Perspect. 2005; 113(4):412–7. [PubMed: 15811831]
47. Kabat GC, et al. Smoking and alcohol consumption in relation to risk of triple-negative breast cancer in a cohort of postmenopausal women. Cancer Causes Control. 2011; 22(5):775–83. [PubMed: 21360045]
48. Ha M, et al. Smoking cigarettes before first childbirth and risk of breast cancer. Am J Epidemiol. 2007; 166(1):55–61. [PubMed: 17426039]
49. Bjerkaas E, et al. Smoking duration before first childbirth: an emerging risk factor for breast cancer? Results from 302,865 Norwegian women. Cancer Causes Control. 2013; 24(7):1347–56. [PubMed: 23633026]
50. Tiede B, Kang Y. From milk to malignancy: the role of mammary stem cells in development, pregnancy and breast cancer. Cell Res. 2011; 21(2):245–57. [PubMed: 21243011]
51. Lyons TR, Schedin PJ, Borges VF. Pregnancy and breast cancer: when they collide. J Mammary Gland Biol Neoplasia. 2009; 14(2):87–98. [PubMed: 19381788]
52. Luo J, et al. Interaction between smoking and obesity and the risk of developing breast cancer among postmenopausal women: the Women's Health Initiative Observational Study. Am J Epidemiol. 2011; 174(8):919–28. [PubMed: 21878422]
53. Rosenberg L, Metzger LS, Palmer JR. Alcohol consumption and risk of breast cancer: a review of the epidemiologic evidence. Epidemiol Rev. 1993; 15(1):133–44. [PubMed: 8405196]

54. Hamajima N, et al. Alcohol, tobacco and breast cancer--collaborative reanalysis of individual data from 53 epidemiological studies, including 58,515 women with breast cancer and 95,067 women without the disease. Br J Cancer. 2002; 87(11):1234–45. [PubMed: 12439712]

55. Haiman CA, et al. Ethnic and racial differences in the smoking-related risk of lung cancer. N Engl J Med. 2006; 354(4):333–42. [PubMed: 16436765]

Table 1

Smoking status by baseline characteristics (age standardized)[a]

Characteristic	Smoking status			
	Never active or passive	Passive only	<5 pack-yrs	≥5 pack-yrs
N	8025	24,172	7,612	11,657
Age, mean	33.9	37.6	39.3	44.7
BMI, %				
<25	44.6	37.1	35.5	33.5
25–29	29.5	31.0	32.2	32.0
≥30	25.0	30.5	30.9	33.3
Years of education, %				
≤12	11.5	16.9	22.1	27.5
13–15	27.9	34.8	39.0	41.6
≥16	60.5	48.2	38.7	30.6
Family history of breast cancer, %	6.4	6.3	6.7	6.7
Age at menarche, %				
≤11	25.7	28.9	27.7	29.3
12–13	54.4	52.2	52.1	51.5
≥14	19.3	18.4	19.7	18.7
Parity, %				
Nulliparous	41.9	36.5	30.3	28.7
1–2	41.4	43.9	48.2	48.6
≥3	16.6	19.4	21.2	22.4
Age at first birth among parous,%				
<20	24.6	31.4	36.1	42.5
20–24	37.2	37.1	35.4	33.1
≥25	37.5	30.8	27.2	23.4
Premenopausal,%	78.2	77.1	76.4	75.0
Postmenopausal, %	15.5	16.5	17.1	18.6
Years of female hormone use, postmenopausal women				
Never used	41.1	40.0	42.9	39.6
<5	30.6	30.9	30.4	31.9
≥5	21.4	23.1	20.3	23.3
Age at menopause, %				
<40	27.2	28.3	27.7	30.6
40–44	19.0	19.5	18.5	20.1
45–49	23.3	22.8	24.5	25.1
≥50	26.9	26.6	26.6	22.1
Yrs of oral contraceptive use, %				
Never used	26.9	23.5	21.7	23.2
<5	42.4	44.4	48.5	46.8
≥5	30.6	32.1	29.8	30.0

Characteristic	Smoking status			
	Never active or passive	Passive only	<5 pack-yrs	≥5 pack-yrs
Hr/wk of strenuous exercise, %				
None	28.4	31.4	30.0	38.8
<5	53.4	51.8	52.4	46.7
≥5	14.2	13.0	13.5	11.4
Drinks/wk of alcohol, %				
<1	85.7	81.7	58.6	58.0
1–3	8.5	10.2	20.2	18.2
≥4	5.2	7.7	20.8	23.4

[a] Percentages may not add to 100% because of missing data

Table 2

Active and passive smoking in relation to breast cancer incidence overall and by menopausal status[a]

Smoking status	All women			Premenopausal		Postmenopausal	
	Cases	P-yrs[b]	IRR (95% CI)	Cases	IRR (95 % CI)	Cases	IRR (95 % CI)
Never active or passive	141	100,184	1.00	70	1.00	52	1.00
Passive only	630	298,822	1.18 (0.98–1.42)	296	1.42 (1.09–1.85)	251	0.92 (0.68–1.24)
Ever smoker	606	251,171	1.08(0.89–1.31)	192	1.21(0.90–1.62)	327	0.86(0.63–1.16)
Former smoker	405	151,751	1.10 (0.90–1.35)	116	1.25 (0.92–1.71)	229	0.84 (0.61–1.15)
Current smoker	201	99,420	1.05 (0.83–1.31)	76	1.14 (0.81–1.61)	98	0.90 (0.63–1.28)

[a] IRRs adjusted for age, questionnaire cycle, BMI, years of education, family history of breast cancer, age at menarche, parity, age at first birth, oral contraceptive use, vigorous exercise, alcoholic beverage consumption, menopausal status, age at menopause, and menopausal female hormone use

[b] Person-years

Table 3

Total pack years and age started active smoking in relation to breast cancer incidence overall and by menopausal status[a]

Pack yrs - Age started	All women			Premenopausal		Postmenopausal	
	Cases	P-yrs[b]	IRR (95% CI)	Cases	IRR (95 % CI)	Cases	IRR (95 % CI)
Never active or passive	141	100,184	1.00	70	1.00	52	1.00
<10 pk-yr	256	126,703	1.05 (0.85–1.30)	98	1.11 (0.81–1.54)	115	0.86 (0.61–1.20)
10–19 pk-yr	150	61,009	1.03 (0.81–1.31)	53	1.37 (0.94–2.00)	83	0.81 (0.57–1.56)
≥20 pk-yr	173	52,214	1.20 (0.95–1.52)	33	1.33 (0.86–2.05)	115	0.92 (0.66–1.30)
Started age <18	219	96,680	1.13 (0.90–1.41)	87	1.35 (0.97–1.88)	98	0.83 (0.58–1.17)
Started age ≥18	379	150,537	1.06 (0.86–1.30)	102	1.11(0.81–1.53)	226	0.88 (0.64–1.20)
<10 pk-yr							
Started age <18	59	39,757	0.93 (0.68–1.27)	28	0.97 (0.62–1.52)	18	0.69 (0.40–1.19)
Started age ≥18	195	85,663	1.11 (0.88–1.38)	69	1.19 (0.84–1.67)	96	0.90 (0.64–1.28)
10–19 pk-yr							
Started age <18	67	27,485	1.17 (0.86–1.57)	31	1.64 (1.05–2.54)	29	0.81 (0.51–1.29)
Started age ≥18	83	33,171	0.96 (0.72–1.27)	22	1.13 (0.69–1.85)	54	0.81 (0.55–1.20)
≥20 pk-yr							
Started age <18	83	26,140	1.28 (0.96–1.70)	24	1.70 (1.05–2.75)	45	0.87 (0.58–1.31)
Started age ≥18	89	25,725	1.14 (0.87–1.61)	9	0.85 (0.42–1.72)	69	0.95 (0.66–1.38)

[a] IRRs adjusted for age, questionnaire cycle, BMI, years of education, family history of breast cancer, age at menarche, parity, age at first birth, oral contraceptive use, vigorous exercise, alcoholic beverage consumption, menopausal status, age at menopause, and menopausal female hormone use

[b] Person-years

Table 4

Total pack-years and duration of active smoking before the first term birth (FTB) in relation to breast cancer incidence overall and by menopausal status among parous women[a]

Pack years and years of smoking before FTB		All women			Premenopausal		Postmenopausal	
		Cases	P-yrs[b]	IRR (95% CI)	Cases	IRR (95 % CI)	Cases	IRR (95 % CI)
Never active or passive		98	57,022	1.00	40	1.00	43	1.00
Pack yrs	Yrs smoked before FTB							
All	<5 yr	137	59,114	1.03 (0.78–1.35)	41	1.47 (0.92–2.33)	75	0.71 (0.48–1.05)
	≥5 yr	209	73,651	1.21 (0.94–1.56)	76	1.54 (1.03–2.30)	100	0.89 (0.61–1.29)
	Smoked after only	145	56,309	1.17 (0.89–1.55)	33	1.33 (0.81–2.19)	94	0.93 (0.63–1.37)
<20	<5 yr	81	41,536	0.93 (0.69–1.27)	32	1.51 (0.93–2.47)	38	0.61 (0.39–0.95)
	≥5 yr	146	55,334	1.20 (0.92–1.56)	57	1.43 (0.83–2.17)	62	0.89 (0.59–1.33)
	Smoked after only	106	42,888	1.20 (0.89–1.61)	30	1.48 (0.89–2.46)	65	0.98 (0.65–1.48)
≥20	<5 yr	52	15,175	1.31 (0.92–1.86)	9	1.64 (0.78–3.46)	35	0.94 (0.59–1.50)
	≥5 yr	56	15,913	1.25 (0.89–1.76)	16	2.01 (1.10–3.65)	34	0.88 (0.55–1.39)
	Smoked after only	31	10,984	1.09 (0.71–1.66)	1	—	24	0.82 (0.49–1.39)

[a] IRRs adjusted for age, questionnaire cycle, BMI, years of education, family history of breast cancer, age at menarche, parity, oral contraceptive use, vigorous exercise, alcoholic beverage consumption, menopausal status, age at menopause, and menopausal female hormone use

[b] Person-years

Table 5

Total pack years of active smoking and started smoking before age 18 in relation to premenopausal breast cancer incidence by body mass index, alcohol consumption, and estrogen receptor status of the tumor[a,b]

Subgroup	Pack yrs and age started	Cases	IRR (95% CI)
BMI <25	Never active or passive	24	1.00
	<20 total	41	1.26 (0.73–2.17)
	≥20 total	14	2.22 (1.09–4.54)
	≥20, started before age 18	12	3.34(1.58–7.05)
BMI ≥25	Never active or passive	46	1.00
	<20 total	110	1.16 (0.81–1.67)
	≥20 total	19	1.01 (0.58–1.77)
	≥20, started at age < 18	12	1.14 (0.59–2.19)
Alcohol drinker	Never active or passive	22	1.00
	<20 total	106	1.29 (0.80–2.06)
	≥20 total	23	1.40 (0.76–2.58)
	≥20, started at age < 18	18	1.85(0.97–3.53)
Nondrinker	Never active or passive	48	1.00
	<20 total	45	1.20 (0.79–1.83)
	≥20 total	10	1.41 (0.70–2.83)
	≥20, started at age < 18	6	1.63 (0.68–3.83)
ER+ cancer	Never active or passive	26	1.00
	<20 total	60	1.37 (0.84–2.23)
	≥20 total	16	1.85 (0.96–3.57)
	≥20, started at age < 18	12	2.58 (1.26–5.29)
ER− cancer	Never active or passive	19	1.00
	<20 total	29	0.96(0.52–1.77)
	≥20 total	4	0.69(0.23–2.09)
	≥20, started at age <18	2	0.59 (0.13–2.58)

[a] IRRs adjusted for age, questionnaire cycle, BMI, years of education, family history of breast cancer, age at menarche, parity, age at first birth, oral contraceptive use, vigorous exercise, alcoholic beverage consumption, menopausal status, age at menopause, and menopausal female hormone use

[b] ER status was obtained for 854 of the 1,377 cases