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Smoking and Survival After Breast Cancer Diagnosis: A Prospective Observational Study and Systematic Review

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Abstract

Background—The association of smoking with outcomes following breast cancer prognosis is not well understood.

Method—In a cohort study called Life After Cancer Epidemiology (LACE), 2265 women diagnosed with breast cancer were followed for a median of twelve years. We used multivariable proportional-hazards models to determine whether smoking, assessed approximately two years post-diagnosis, was associated with risk of death among these women. We also undertook a systematic review of all cohort studies to date that have examined the association between smoking and breast cancer mortality.

Results—Compared with never smokers, women who were current smokers had a two-fold higher rate of dying from breast cancer [hazard ratio (HR)=2.01, 95% confidence interval (CI) 1.27–3.18] and an approximately four-fold higher rate of dying from competing (non-breast cancer) causes (HR=3.84, 95%CI 2.50–5.89). Among seven studies that met the inclusion criteria in the systematic review, three studies and our own reported significantly increased risk of breast cancer death with current smoking. We found little evidence of an association between former smoking and breast cancer mortality (HR=1.24, 95% CI 0.94–1.64).

Conclusions—Consistent with findings from our prospective observational study, the systematic review of seven additional studies indicates positive association of current smoking with breast cancer mortality, but weak association with former smoking.

Impact—Women who smoke following breast cancer diagnosis and treatment are at higher risk of death both from breast cancer and other causes.

Keywords

Cigarette smoking; breast cancer; survival; cohort study; systematic review

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INTRODUCTION

Breast cancer is a highly heterogeneous disease with large variations in survival[1]. Identification of modifiable lifestyle factors that may improve survival is of interest to women diagnosed with breast cancer as well as their caregivers. Smoking has been associated with increased mortality following diagnosis of a variety of cancers, including prostate[2,3], colorectal[4] and vulvar[5] cancers, leukemia[6] and malignant melanoma[7]. Smoking after breast cancer diagnosis has been shown to adversely affect overall survival[8,9], whereas the association with breast cancer specific survival appears equivocal [10,11,9,12,13]. Smoking is associated with several factors that lead to poorer outcomes among women with breast cancer, including lower socioeconomic status[14,15], decreased physical activity[16,17] and comorbidity[18,19]. Comorbidity may be the most life-threatening issue among women with breast cancer who are current or former smokers because of an increased mortality risk from a spectrum of smoking-associated conditions and the fact that comorbidity can often lead to receiving less aggressive or less complete cancer treatment [20].

Wells[21] hypothesized that inconsistent epidemiologic evidence for the association of smoking with breast cancer may reflect both adverse and protective effects of smoking. Evidence for the adverse effects comes from work implicating smoking in increased metastatic potential of cancer cells and promotion of tumor angiogenesis and growth[22]; protective effects, however, may work through the anti-estrogenic effects of smoking[21]. The hypothesis that smoking may induce earlier menopause thus reducing the risk of breast cancer has received inconsistent support [23–26]. Subsequent epidemiological studies have shown either no association or a small increase in risk of breast cancer associated with active smoking [27,25,28]. Some support for the association of smoking with breast cancer risk comes from a recent laboratory study indicating that nicotine receptor mediated carcinogenic properties are involved in biological functions associated with the development of breast cancer [29].

Based on the biological and epidemiological evidence that smoking may influence breast cancer progression, we hypothesized that smoking would be associated with both an increased risk of death from breast cancer as well as from other causes in our prospective cohort of more than 2,000 women with breast cancer. In this study of the relationship of smoking with mortality, we considered death from breast cancer, competing causes and all causes for women in the National Cancer Institute funded population-based cohort of predominantly early stage breast cancer survivors, Life After Cancer Epidemiology (LACE [30]). This large cohort of over 2,000 breast cancer survivors was well suited to examining the consequences of cigarette smoking following initial breast cancer treatment while taking into account known prognostic factors in the clinical, lifestyle-related and sociodemographic domains. We assessed the extent to which the impact of smoking on survival differed as a function of tumor subtype [estrogen receptor (ER), progesterone receptor (PR) and Human Epidermal Growth Factor Receptor 2 (HER2) status], body mass index and menopausal status. To place our study-specific results in the context of the current evidence base, we also undertook a systematic review of all cohort studies to date that have examined the association between smoking and breast cancer mortality.

METHODS

Study population

The LACE cohort consists of women diagnosed with stage I (≥1 cm), II, or IIIa breast cancer from 1997 to 2000 in the Kaiser Permanente Northern California (KPNC) Cancer Registry or the Utah Cancer Registry. Eligible women were diagnosed, on average 21

months (range 9–39 months) prior to enrollment, had completed completed breast cancer treatment (except adjuvant hormonal therapy) and were free of any documented recurrence during that period. In addition to the KPNC and Utah cancer registries, this cohort included women screened and eligible for the Women's Healthy Eating and Lifestyle (WHEL) study, a dietary intervention trial examining the prevention of breast cancer recurrence. A total of 2,586 (45.7%) completed initial enrollment; subsequent review to confirm eligibility left 2,270 women in the cohort. The large majority of cohort members (82%) came from KPNC, 12% from Utah, and 6% from WHEL. The upper age restriction for enrollment to the study was 79 years. Of 2,270 women included in the cohort, data on smoking status was available for 2, 258 participants (Table 1). This final sample formed the study population in the present analysis.

The Institutional Review Boards at the University of California, San Francisco and the KPNC approved this study.

Smoking assessment

Smoking status was determined from baseline questionnaire that was completed on average 23 months (ranging from 11 to 39 months) after breast cancer diagnosis. The questionnaire asked whether they currently smoked cigarettes and whether they had ever smoked in the past. "Never smokers" were women who answered "no" to both questions. Women were also asked if they consumed more than 100 cigarettes in their lifetime; we will refer to this measure as "ever-smoking". Those that responded affirmatively were additionally asked the average number of cigarettes smoked per day.

Outcome ascertainment

A health status update questionnaire was mailed to LACE participants to monitor health outcomes semi-annually until April 2006 and annually thereafter until June 2012. The health status update asked women about any events that might have occurred in the preceding 6 months (or 12 months on the revised questionnaire), including recurrences or new primary breast cancer, hospitalizations, and other cancers. Reported events were confirmed by medical record review. Participant deaths were determined through KPNC electronic data sources, a family member responding to a mailed questionnaire, or by phone call to a proxy. All reported deaths were confirmed by death certificate review to verify primary and underlying cause of death. This information was then categorized as breast cancer death or non-breast cancer death. Outcomes were updated regularly by surveillance of KPNC electronic data sources and mortality files (including data from the States of California and Utah Departments of Vital Statistics and the U.S. Social Security Administration) for all participants, including those who dropped out (n = 90) or were lost to active follow-up (n = 15). In this analysis, the outcomes of interest were mortality from breast cancer, other causes and all causes.

Covariates

The covariates in these analyses were socio-demographic, lifestyle-related, and clinical prognostic factors that, based on the existing literature and *a priori* reasoning, could potentially confound an association between smoking status and mortality. The sociodemographic covariates included age (calculated as the difference between date of breast cancer diagnosis and reported date of birth), race/ethnicity (white, non-white), and education (≤ 12 years, 13–15 years, >15 years). Lifestyle-related factors included body mass index (BMI) at diagnosis (calculated as weight in kilograms/height in meters squared, or kg/m^2, from self-reported weight and height), physical activity at enrollment, and alcohol consumption (≤0.5 g/day, 0.6–5 g/day, ≥ 6 g/day). Standard BMI categories (normal weight, < 25; overweight, 25 – 30, and obese, ≥ 30) were used[31]. Physical activity was assessed

with a questionnaire based on the Arizona Activity Frequency Questionnaire [32]. Standard metabolic equivalent task (MET) values were assigned to each activity and then frequency was multiplied by duration and MET value and summed over all activities (other than the sedentary recreational and transportation activities), providing a summary measure of total activity in MET hours per week [33]. Two categories of physical activity, above and below the median in this group, were used (≤46 MET-hours/week, >46 MET-hours/week).

Prognostic factors were obtained from medical chart review and electronic databases for the LACE participants who were KPNC members and from medical chart review only for those who were not, and included menopausal status (pre-menopausal, post-menopausal, missing), lymph node involvement (0, 1–3, ≥4), estrogen receptor (ER) status (positive, negative, missing), progesterone receptor (PR) status (positive, negative, missing), and human epidermal growth factor 2 (HER2) receptor status (positive, negative, missing) from primarily immunohistochemistry, chemotherapy treatment (yes/no), radiation treatment (yes/no), tamoxifen use (never user, former user, current user, missing), and type of surgery (conserving or mastectomy). Stage at diagnosis (I, IIA, IIB, IIIA) was classified according to the Tumor, Node, Metastasis (TNM) system based on the criteria of the American Joint Committee on Cancer[34]. Multivariate models for all-cause and non-breast cancer mortality were further adjusted for comorbidity. Patient-reported comorbid medical conditions were used as an indicator of the comorbidity burden; these conditions included thyroid disease, hypoglycemia, diabetes, hypertension, myocardial infarction, angina, peripheral arterial disease, gallbladder disease, diverticulitis, Crohn disease, pancreatitis, colorectal polyps, irritable syndrome, kidney disease, arthritis, osteoporosis, cirrhosis, stroke, and lupus. The comorbidity burden was estimated using the Charlson comorbidity index (CCI[35,36]). The CCI was derived from the number and type of underlying diseases present at study entry from patient questionnaire data and was categorized as a binary variable (0, ≥1).

Statistical analysis

Differences in means and proportions of selected covariates in the exposure groups were assessed using Student *t* test for continuous variables and Pearson χ^2 for categorical variables. For categorical covariates with fewer than 5 participants in one or more categories, Fisher's exact test was used instead of Pearson χ^2. Kaplan-Meier plots were used to examine associations between smoking status and survival graphically and statistically respectively. Follow-up began at the time of diagnosis and ended at first confirmed date of death, depending on the specific analysis. Individuals who were alive were censored at the date of last contact (either most recent health status update questionnaire or electronic surveillance). Guided by *a priori* considerations [37], separate delayed-entry Cox proportional hazards models [38,39] with time since diagnosis as the time scale were used to estimate the risk of each outcome associated with smoking status and ever-smoking, accounting for varying times of enrollment into the cohort, and adjusting for covariates. Risk was expressed as a hazard ratio and 95% confidence interval (CI). The type I error was set at .05 and all reported *P*-values are two-sided.

After generating unadjusted Cox proportional hazards models for smoking status, known prognostic variables and those that showed significant relations with either the independent or dependent variable were added to the model ($p<0.10$). All Cox models were tested for proportionality of hazards graphically and statistically [40]. In multivariate models, interaction terms were considered. All analyses were conducted in SAS version 9.2 and R version 2.15.0.

Systematic review

We identified papers published prior to July 1st, 2012 through a search in Medline (www.ncbi.nlm.nih.gov) and Google (www.google.com) using the following search terms: 'smoking or tobacco', 'mortality or survival' and 'breast (neoplasm or cancer)'. We also performed a cited-reference search of retrieved articles and identified publications by review of the references in the retrieved articles. For each of the studies included in the review we abstracted characteristics of the study population; information on follow-up; outcome, exposure and covariate assessment; results and conclusions. We followed the PRISMA guidelines (http://www.prisma-statement.org; Transparent Report of Systematic Reviews and Meta-Analysis[41]) as a methodological template for this review (see Figure 1 and Appendix 1).

Inclusion criteria—We included studies with the following characteristics: (i) included women diagnosed with invasive breast cancer and of at least 18 years of age at diagnosis; (ii) included a measure of smoking status categorized as current-, past- and never-smokers; (iii) considered breast cancer-specific mortality as one of the outcomes; and (iv) were of cohort design.

Exclusion criteria—We excluded studies that were published in languages other than English, and for which full text was not available. Intervention studies of smoking cessation in breast cancer survivors were also excluded.

A flow diagram of our literature search algorithm is provided in Figure 1. For each of the studies included in the review we abstracted characteristics of the study population; information on follow-up; outcome, exposure and covariate assessment; results and conclusions were.

RESULTS

Distributions of baseline characteristics for selected variables by smoking status are presented in Table 1. At study initiation 52.9% (1194/2258) of the study participants reported that they had never smoked, 39.5% (891/2258) were former smokers, and 7.7% (173/2258) were current smokers. The majority of the women were early-stage breast cancer survivors with 81% in stages I or IIa at the time of diagnosis. The median age was 58 years (SD=11.0 years; range 25–79 years) at the time of breast cancer diagnosis; 20% of the participants were non-white and nearly 27.4% had a high school level education or below. Never and former smokers tended to be older, and more educated than current smokers.

We noted a significant variation in the distribution of tumor stage (p-value=0.02): 83.2% of current, 81.9% of former and 78.7% of never smokers had stage I or IIa disease. Current and former smokers were more likely to have HER2 negative tumors compared to never smokers (78%, 79.7% and 71.9% respectively, p-value=0.002). Significant differences were also observed in menopausal status with 60.1% of never, 69.7% of former, and 56.6% of current smokers reporting post-menopausal status (p-value<0.0001). Former and current smokers were more likely to consume larger quantities of alcohol than never smokers: 28.3% of current smokers and 30.0% of former smokers consumed more than 6 grams of alcohol per day compared to 13.5% of never smokers (p-value<0.0001). Never smokers were also more likely to receive chemotherapy than former or current smokers (60.6% vs. 52.6% and 56.6% respectively, p-value=0.002).

The median follow-up in our analytic cohort of 2,258 women was 12.3 years (standard deviation=2.9 years; range 1.5–15.5 years). The median follow-up among current smokers was significantly shorter than the median follow-up among former and never smokers (11.9

vs. 12.2 vs. 12.4 years respectively; p=0.0005). During this period, a total of 485 deaths was observed: 215 among 1194 never smokers, 213 among 891 former smokers, and 57 among 173 current smokers. Of these 485 deaths, 241 of deaths were due to other causes (105 among never smokers, 105 among former smokers, and 32 among current smokers) and 244 were due to breast cancer (111 among never smokers, 108 among former smokers and 25 among current smokers).

Kaplan-Meier plots of survival by smoking status for all-cause survival (Figure 2a), competing-cause survival (Figure 2b), and breast cancer-specific survival (Figure 2c) revealed differences by smoking status in all-cause, competing-cause, and to lesser extent in breast cancer survival. In Table 2, we present results indicating that current smokers had significantly higher risk of all-cause, competing-cause and breast cancer-specific mortality than never smokers. Current smokers had an increased risk of death from any cause in unadjusted (HR=2.03, 95% CI 1.51–2.72), and covariate-adjusted models (HR=2.63, 95% CI 1.93–3.58). Former smoking was also associated with increased risk of all-cause mortality in both unadjusted (1.38, 95%CI 1.14–1.67) and covariate-adjusted models (1.28, 95%CI 1.05–1.56). Both current and former smoking were associated with increased risk of competing-cause mortality, with covariate-adjusted hazard ratios of 3.84 (95%CI 2.50–5.89), and 1.33 (1.00, 1.78), respectively. Compared to never smokers, current smokers had an approximately two-fold increase in the risk of breast cancer death in unadjusted (HR=1.71, 95%CI 1.11–2.64), and covariate-adjusted models (HR=2.01, 95%CI 1.27–3.18). Former smoking was associated with increased risk of breast cancer mortality in unadjusted models (HR=1.35, 95%CI 1.04–1.76). After adjusting for all potential confounders, the association was attenuated and did not reach statistical significance (HR=1.24, 95%CI 0.94–1.64). We further examined the association between ever-smoking and all mortality outcomes and found similar magnitude and direction of associations (data not shown).

We next examined whether tumor characteristics such as ER, PR and HER2, menopausal status, and BMI at cohort entry modified the effect of smoking on breast cancer mortality. When interaction terms were included in multivariate models, we found significant interactions with normal BMI (p-value= 0.003), and HER2 positivity (p-value=0.02), but not with ER, PR and menopausal status. Stratified analyses revealed increased risk of breast cancer death in current smokers with both ER positive and negative tumors (Table 3); the association did not reach statistical significance among those with ER negative tumors, likely due to the small number of breast cancer deaths in this group. We found no evidence of effect modification by PR or HER2 status.

Possible variations in the effect of smoking status on breast cancer survival according to BMI were also evaluated (Table 3). Fully adjusted models suggest that both current and former smoking increases the risk of breast cancer death across all BMI strata. While the association was statistically significant among current smokers (HR=4.46, 95%CI 2.03–9.76) and former smokers (HR=1.70, 95%CI 1.00–2.90) of normal weight (BMI<25), the association did not reach statistical significance among overweight and obese women (BMI ≥25) who were former or current smokers.

We next evaluated whether the association of smoking status with breast cancer mortality varied according to menopausal status. We found an increased risk of breast cancer death in pre and postmenopausal women who were current smokers (Table 3). Among former smokers, we found an increased risk of breast cancer mortality among pre-menopausal women (HR=2.73, 95%CI 1.40–5.32), but not post-menopausal women.

For the systematic review, we identified six published cohort studies of the association, and these are summarized in Table 4 together with our own study. In general, we observed

increased a stronger risk of breast cancer mortality among women with breast cancer who were current smokers than among those who were former smokers. Notably, three of the seven studies in the systematic review reported risk ratios for estimates of breast cancer mortality and four reported hazard ratios for this outcome. Given these differences in the effect measures reported, we chose not to combine the studies quantitatively using meta-analysis.

DISCUSSION

Our prospective observational study shows that smoking following breast cancer diagnosis and treatment is detrimental not only to overall and non-breast cancer mortality but also to breast cancer specific mortality in women diagnosed with breast cancer. While former smoking affects non-breast cancer mortality, we found little evidence that former smoking increases the risk of breast cancer-specific mortality. We evaluated whether the association of smoking status with breast cancer mortality varied according to menopausal status and found that both premenopausal current and former smokers were at increased risk of breast cancer death, which is consistent with a recently published study[13]. The association of current smoking with breast cancer-specific mortality was stronger among women of normal weight (BMI<25) than among overweight and obese women (BMI ≥25).

Of the seven prospective observational studies in our systematic review that examined current versus never smoking and breast cancer mortality, three large studies[9,42,13] and our own study indicated a positive association. Although none of the seven studies in our systematic review demonstrated a statistically significant association between former smoking and the risk of breast cancer death, the effect estimates were elevated in four reports and our own study (Table 4). We extend the literature on smoking and risk of death after breast cancer diagnosis to clarify that the association is stronger with current than with former smoking. The small number of primary studies in this systematic review precluded pooling of the results using meta-analysis; it also precluded an examination of subgroups and potential modifying effects of BMI, tumor subtype, and menopausal status in the association of smoking with mortality following breast cancer diagnosis.

The link between smoking and breast cancer risk or mortality has attracted considerable research attention. Ambrosone *et al.* [43] reported that only those postmenopausal women with the slow acetylation phenotype of the *polymorphic* Nacetyltransferase 2 (NAT2) *gene* showed an association between active smoking and incident breast cancer risk; fast acetylators showed no association. Among postmenopausal slow acetylators, Morabia *et al.* [44] reported that active smokers had a significantly higher breast cancer risk than never smokers whereas among premenopausal women, there were no significant differences in the relative risk of breast cancer between slow and rapid acetylators who were active versus never smokers.

Since breast cancer is a highly heterogeneous disease[1], it is plausible that smoking differentially affects estrogen-responsive tumors versus more aggressive forms of cancer. In addition, cigarette smoke has been associated with elevated metastatic potential of tumor cells and stimulation of angiogenesis [22]. The association of cigarette smoke with increased pulmonary metastatic propensity in mouse models [45] gives rise to the hypothesis that smoking could increase the risk of breast cancer recurrence and death. Consistent with this, cross-sectional epidemiologic evidence has shown that smokers with breast cancer had more and larger lymph node metastases than nonsmokers, after controlling for primary tumor size and other variables [46–48]. In addition, smoking has been associated with a younger age at diagnosis [49], hormone receptor negative breast cancer [50] and an increased risk of lung metastases among breast cancer patients [45,51]. Although mechanisms that lead to the

altered tumor behavior associated with smoking are not well established, it has been shown that some complications of radiation therapy may be more frequent and severe in smokers [52]. Notably, never smokers were more likely to receive chemotherapy than current or former smokers. Analysis of smoking status among women undergoing breast cancer treatment may help better target therapeutic options.

A limitation of our study is that smoking status was self-reported and lacked details of the number of packs consumed and whether smoking continues throughout the follow-up period. Hence, we were unable to evaluate a dose-response relationship between smoking and outcomes, or evaluate the effect of change in smoking status later after breast cancer diagnosis. We were also unable to investigate age of starting smoking and how that factor may influence outcomes after breast cancer diagnosis. The proportion of women who were current smokers at the time of enrollment was low. In addition, smoking status and other measures were self-reported, and self-reported smoking exposures were not validated by smoking biomarkers. Since former smokers were likely motivated by a breast cancer diagnosis to stop smoking, relatively few current smokers were identified at the time of enrollment. It is important to note that the finding of this study regarding current smoking and breast cancer-specific survival was based on only 25 events in current smokers, thus in spite of statistical significance is liable to uncertainty. Our analyses consider cancer deaths, which may also reflect the role of smoking on cancer diagnosis or treatment rather than the direct effect of smoking on cancer mortality. Another potential limitation is the possible misclassification of cause of death. If some of the breast cancer deaths are in fact deaths from other causes, we would find at least some positive association with smoking and breast cancer mortality because deaths would include those from smoking-related conditions such as cardiovascular disease or lung cancer. Finally, we were also unable to evaluate the role of smoking in the development of any metastases.

The strengths of the study include its prospective population-based cohort design, its large size and our ability to take into account multiple covariates in the tumor-related, lifestyle and socio-demographic domains. In addition, information on molecular subtypes allowed us to compute subtype-specific estimates of association between smoking and breast cancer mortality. Efforts to investigate this question further should include additional investigations of smoking and subtype-specific mortality in studies with more detailed data on the intensity and duration of smoking exposure and a larger sample size for evaluating outcomes stratified by tumor subtype.

In conclusion, the results from this large cohort study and systematic review add to the scant evidence examining the association of smoking with mortality after breast cancer diagnosis. Taking the results of our cohort study and systematic review together, we have found evidence for a positive association of current smoking with breast cancer mortality. The evidence for an effect of former smoking on breast cancer mortality is weak. In addition, a stronger association was observed between current smoking and overall mortality than breast cancer-specific mortality. While this work is unable to provide a definitive answer on the nature of the relationship between smoking and breast cancer mortality, it provides more support for the importance of current than former smoking. In addition, the stronger association was observed between current or former smoking and overall mortality. As is the case in survivors of other cancer and in the general population, these results underscore the importance of promoting smoking cessation efforts among breast cancer survivors. Our data suggest that for breast cancer survivors who are current smokers, reduction in breast cancer mortality may be yet another motivation for smoking cessation.

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Appendix 1

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	NA
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language,	7

Section/topic	#	Checklist item	Reported on page #
		publication status) used as criteria for eligibility, giving rationale.	
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	7
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	7
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	NA
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	NA
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	NA
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	NA
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	NA
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	NA
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	NA
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Figure 2
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 4
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	NA
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Table 4
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	NA
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	NA
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	NA
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	10

Section/topic	#	Checklist item	Reported on page #
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	10
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	12
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

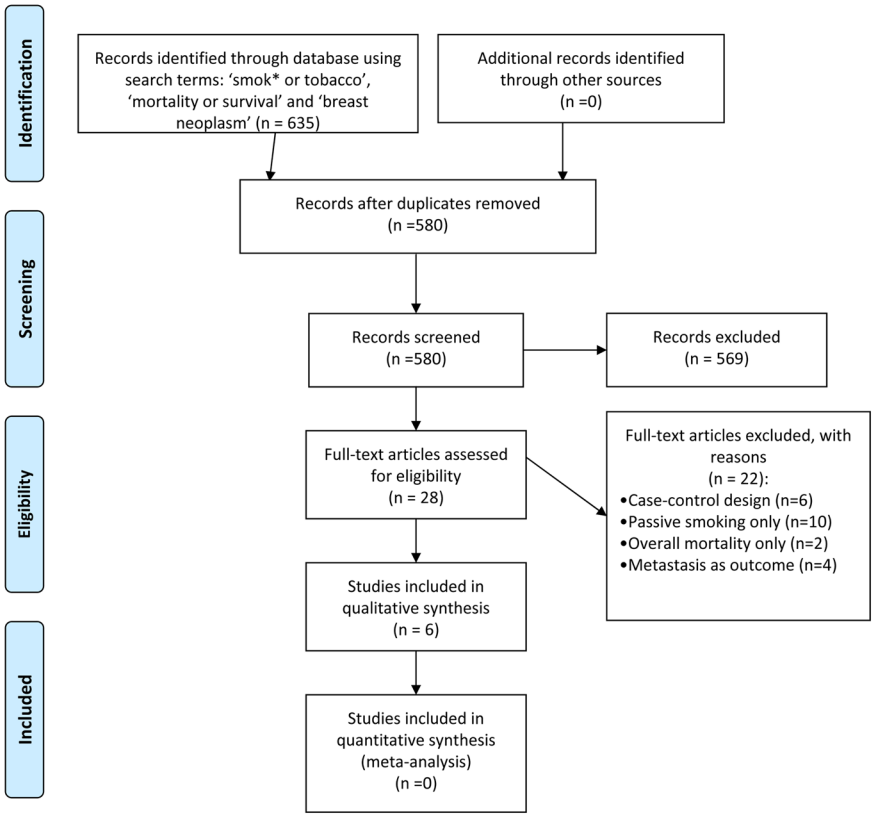


FIGURE 1.

PRISMA flow diagram* of literature search for the association between smoking status and breast cancer mortality

*The PRISMA flow diagram depicts the flow of information throughout the different phases of this systematic review. It includes the number of records identified, included, and excluded and the reason for exclusions.

Figure 2a

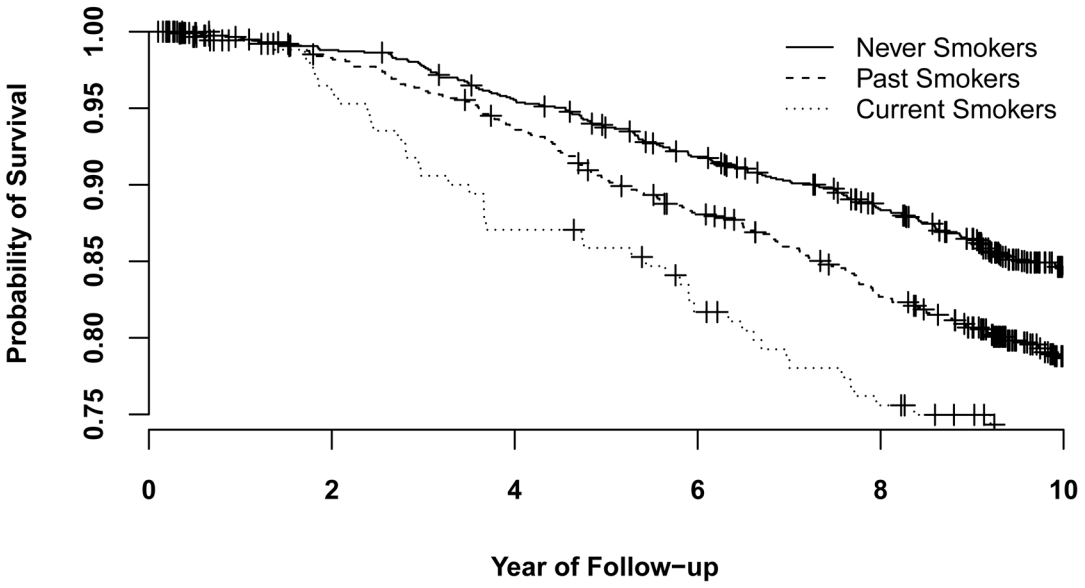
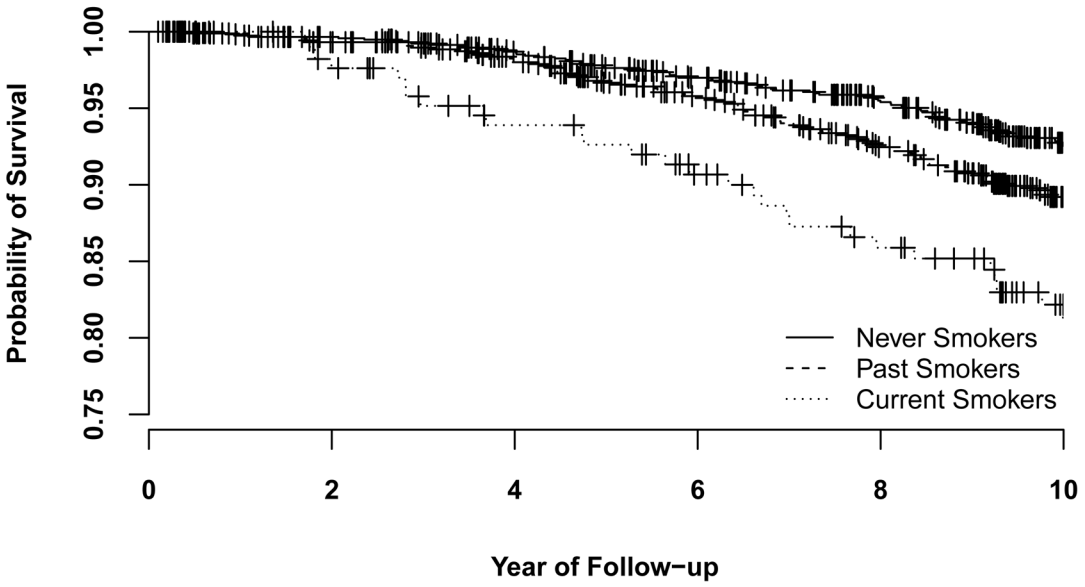


Figure 2b



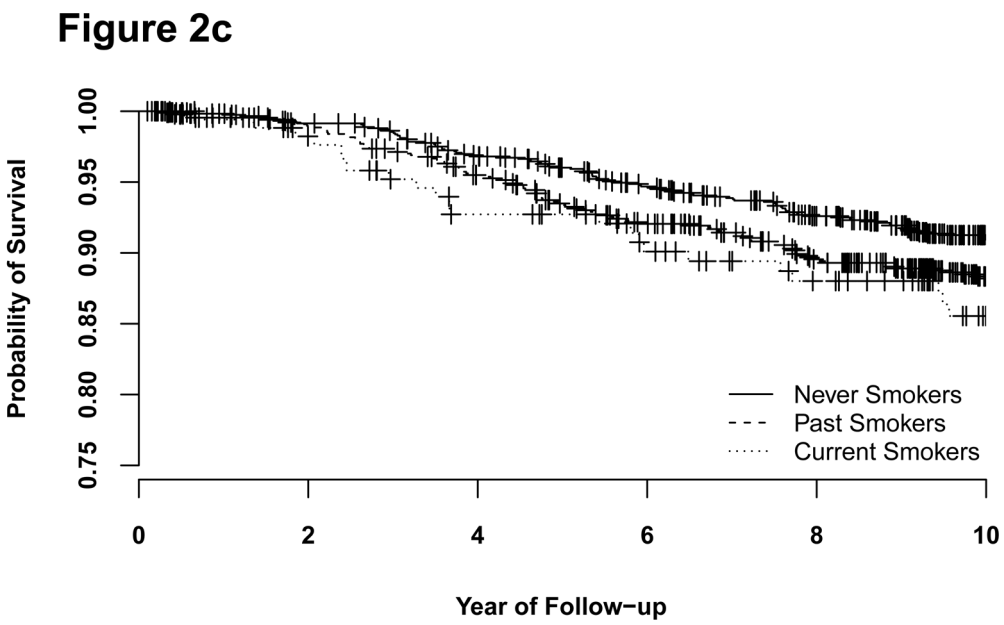


FIGURE 2.
Kaplan-Meier plots of survival, by smoking status
(a) All-cause survival
(b) Other cause survival
(c) Breast cancer survival

Table 1

Study characteristics by smoking status among women with breast cancer

	Never Smokers N=1194 (52.9%)	Former Smokers N=891 (39.5%)	Current Smokers N=173 (7.7%)	P Value‡
Follow-up, Median (Q1, Q3)	12.4 (11.4, 13.3)	12.2 (10.8, 13.4)	11.9 (9.3, 13.2)	0.0005
Sociodemographic Factors				
Age at diagnosis, mean±SD	57.5 ± 11.4	60 ± 10.2	54.6 ± 10.3	<.0001
Education, n (%)				
≤high school	317 (26.5)	240 (26.9)	61 (35.3)	
College	639 (53.5)	467 (52.4)	93 (53.8)	0.002
Graduate	236 (19.8)	181 (20.3)	18 (10.4)	
Race/ethnicity, n (%)				
White	927 (77.6)	734 (82.4)	143 (82.7)	
Black	56 (4.7)	42 (4.7)	14 (8.1)	
Hispanic	82 (6.9)	51 (5.7)	8 (4.6)	<.0001
Asian	99 (8.3)	28 (3.1)	2 (1.2)	
Other	29 (2.4)	35 (3.9)	5 (2.9)	
Prognostic Factors				
Stage, n (%)				
Stage I	527 (44.1)	432 (48.5)	93 (53.8)	
Stage IIA	413 (34.6)	298 (33.4)	51 (29.5)	0.02
Stage IIB	219 (18.3)	128 (14.4)	27 (15.6)	
Stage IIIA	34 (2.8)	33 (3.7)	2 (1.2)	
Number of lymph nodes involved, n (%)				
0	727 (60.9)	586 (65.8)	112 (64.7)	
0–3	332 (27.8)	215 (24.1)	43 (24.9)	0.91
4+	92 (7.7)	72 (8.1)	12 (6.9)	
ER receptor status, n (%)				
Negative	223 (18.7)	144 (16.2)	26 (15)	
Positive	961 (80.5)	741 (83.2)	145 (83.8)	0.41
Unknown	10 (0.8)	6 (0.7)	2 (1.2)	
PR receptor status, n (%)				

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	Never Smokers N=1194 (52.9%)	Former Smokers N=891 (39.5%)	Current Smokers N=173 (7.7%)	P Value‡
Negative	369 (30.9)	245 (27.5)	55 (31.8)	
Positive	814 (68.2)	640 (71.8)	116 (67.1)	0.34
Unknown	11 (0.9)	6 (0.7)	2 (1.2)	
HER2 receptor status, n (%)				
Negative	858 (71.9)	710 (79.7)	135 (78)	
Positive	181 (15.2)	123 (13.8)	22 (12.7)	0.002
Unknown	155 (13)	58 (6.5)	16 (9.2)	
Menopausal status at diagnosis, n (%)				
Pre-menopausal	317 (26.5)	149 (16.7)	46 (26.6)	
Post-menopausal	717 (60.1)	621 (69.7)	98 (56.6)	<.0001
Unknown	160 (13.4)	121 (13.6)	29 (16.8)	
Physical health/lifestyle				
Body mass index (kg/m^2), n (%)				
<25	403 (33.8)	286 (32.1)	50 (28.9)	
25–30	328 (27.5)	273 (30.6)	47 (27.2)	0.38
>30	288 (24.1)	188 (21.1)	40 (23.1)	
Physical activity (MET hours/wk), n (%)				
≤46	668 (55.9)	511 (57.4)	109 (63)	0.59
>46	526 (44.1)	380 (42.6)	64 (37)	
Alcohol consumption (g/d), n (%)				
≤0.5 g/d	775 (64.9)	434 (48.7)	94 (54.3)	
0.6–5.0 g/d	258 (21.6)	190 (21.3)	30 (17.3)	<.0001
≥ 6 g/d	161 (13.5)	267 (30)	49 (28.3)	
Charlson comorbidity, n (%)				
0	528 (44.2)	349 (39.2)	78 (45.1)	0.06
1+	578 (48.4)	475 (53.3)	84 (48.6)	
Treatment				
Chemotherapy received	723 (60.6)	469 (52.6)	98 (56.6)	0.002
Radiation received	760 (63.7)	562 (63.1)	97 (56.1)	0.20
Surgery				
Conserving	604 (50.6)	460 (51.6)	79 (45.7)	0.38

	Never Smokers N=1194 (52.9%)	Former Smokers N=891 (39.5%)	Current Smokers N=173 (7.7%)	P Value‡
Mastectomy	590 (49.4)	431 (48.4)	94 (54.3)	
Tamoxifen				
Never	257 (21.5)	192 (21.5)	48 (27.7)	
Past	72 (6)	67 (7.5)	14 (8.1)	0.20
Current	857 (71.8)	630 (70.7)	109 (63)	

‡P-values were computed using Student *t* test for continuous variables and Pearson χ^2 for categorical variables. For covariates with fewer than 5 participants in one or more categories, Fisher's exact test was used instead of Pearson χ^2.

Table 2

Hazard ratios and 95% CIs for the effect of smoking on mortality among women with breast cancer

Outcome	Never Smokers N=1194	Former Smokers N=891	Current Smokers N=173
Breast cancer-specific mortality	**deaths=111**	**deaths=108**	**deaths=25**
Unadjusted model	Reference	1.35 (1.04,1.76)	1.71 (1.11,2.64)
Model 1 *	Reference	1.24 (0.94,1.64)	2.01 (1.27,3.18)
All-cause mortality	**deaths=215**	**deaths=213**	**deaths=57**
Unadjusted	Reference	1.38 (1.14,1.67)	2.03 (1.51,2.72)
Model 2 **	Reference	1.28 (1.05,1.56)	2.63 (1.93,3.58)
Other cause mortality	**deaths=105**	**deaths=105**	**deaths=32**
Unadjusted	Reference	1.41 (1.07,1.85)	2.37 (1.59,3.52)
Model 2 **	Reference	1.33 (1.00,1.78)	3.84 (2.50,5.89)

* **Model 1:** Adjusted for age at diagnosis (continuous), education (≤ 12 years, 13–15 years, >15 years), race/ethnicity (white, non-white), chemotherapy treatment (yes/no), radiation treatment (yes/no), tamoxifen (never user, former user, current user, missing), type of surgery (conserving/mastectomy), estrogen receptor (positive, negative, missing), progesterone receptor (positive, negative, missing), HER 2 receptor (positive, negative, missing), menopausal status (pre-menopausal, post-menopausal, missing), body mass index in kg/m^2 (<25, 25–29.9, ≥30, missing), stage (I, IIA, IIB, IIIA), physical activity in MET-hours/week (≤ 46, >46), nodal involment (0, 1–3, ≥4), and alcohol consumption (≤0.5 g/day, 0.6–5 g/day, ≥ 6 g/day).

** **Model 2:** Same as Model 1 plus level of comorbidity (0 Charlson comorbidity, 1+ Charlson comorbidity)

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Table 3

Covariate adjusted hazard ratios for the effect of smoking on breast cancer mortality stratified by tumor characteristics, body mass index, and menopausal status*

	Never Smokers			Former Smokers			Current Smokers		
	N	Deaths	HR (95% CI)	N	Deaths	HR (95% CI)	N	Deaths	HR (95% CI)
Tumor characteristics									
Estrogen receptor status									
Negative	223	24	1	144	16	0.84 (0.42,1.70)	26	5	2.51 (0.86,7.38)
Positive	961	87	1	741	91	1.30 (0.95,1.77)	145	19	1.80 (1.06,3.05)
Progesterone receptor status									
Negative	369	39	1	245	27	0.88 (0.52,1.50)	55	10	2.03 (0.95,4.34)
Positive	814	72	1	640	80	1.32 (0.94,1.84)	116	14	1.58 (0.85,2.94)
HER 2 status									
Negative	858	79	1	710	81	1.13 (0.82,1.56)	135	18	1.58 (0.92,2.72)
Positive	181	19	1	123	22	1.54 (0.76,3.14)	22	2	1.49 (0.33,6.83)
Body mass index									
<25	578	51	1	430	56	1.70 (1.00,2.90)	86	16	4.46 (2.03,9.76)
≥25	616	60	1	461	52	1.17 (0.84,1.62)	87	9	1.44 (0.79,2.63)
Menopausal Status									
Post-menopausal	717	75	1	621	73	1.09 (0.78,1.53)	98	17	1.81 (1.03,3.17)
Pre-menopausal	317	22	1	149	21	2.73 (1.40,5.32)	46	6	2.83 (1.00,8.01)

*Adjusted for age at diagnosis (continuous), education (≤ 12 years, 13–15 years, >15 years), race/ethnicity (white, non-white), chemotherapy treatment (yes/no), radiation treatment (yes/no), tamoxifen (never user, former user, current user, missing), type of surgery (conserving/mastectomy), estrogen receptor (positive, negative, missing), progesterone receptor (positive, negative, missing), HER 2 receptor (positive, negative, missing), menopausal status (pre-menopausal, post-menopausal, missing), body mass index in kg/m2 (<25, 25–29.9, ≥30, missing), stage (I, IIA, IIB, IIIA), physical activity in MET-hours/week (≤ 46, >46), nodal involment (0, 1–3, ≥4), and alcohol consumption (≤0.5 g/day, 0.6–5 g/day, ≥ 6 g/day). When modification by a given factor was assessed, this factor was not included as a covariate in multivariate models.

Table 4

Systematic review of smoking and breast cancer mortality

First author, year (reference no)	Population	Assessment of smoking	Length of follow-up from smoking assessment till death or loss to follow-up	No. of breast cancer deaths	Main results	Adjustments
			Cohort studies		**RR (95% CI)**	
Calle et al. 1994 (9)	604,412 women from the Cancer PrevetionStudy II, who were cancer free at interview in 1982. Median age at study initiation was 56 years; 75% of the women were between 45 and 70 years of age, and none were younger than 30. 319,446 women were never smokers and 254,122 were current or former smokers.	Reported in interview	Women were followed for 6 years	Never Smokers: 468 Ever Smokers: 346	Never: 1.00 Former and Current: 1.02 (0.88–1.19)	Adjusted for family history of breast cancer, body mass index, education, alcohol, breast cysts, age at first birth, age at menarche, and age periods stopped
Manjer et al. 2000 (41)	742 Women with breast cancer diagnosed in the Malmö mammographic screening trial between 1977 and 1986. 491 women were never smokers, 216 women were current smokers, and 85 womenwere former smokers.	Review of hospital records	Mean follow-up was 12.1 years. Never smokers contributed 6014 person years, Former smokers contributed 1072 person years, and current smokers contributed 2473 person years of follow-up.	Never Smokers: 81 Former Smokers: 16 Current Smokers: 48	Never: 1.00 Former: 1.28 (0.60–2.74) Current: 1.95 (1.22–3.13)	Adjusted for stage and menopausal status
Holmes at al. 2007 (10)	5,056 women from the Nurses' Health Study with Stages I–III invasive breast cancer diagnosed between 1978 and 2002. 2,112 women were never smokers, 1926 women were former smokers, and 1018 women were current smokers. Mean age at diagnosis was 59.2 for never smokers, 60.2 for former smokers, and 56.8 for current smokers.	Reported in biannual questionnaire immediately following breast cancer diagnosis	46,535 person years of follow-up, with a median follow-up of 8.25 years	Never Smokers: 357 Former Smokers: 255 Current Smokers: 216	Never: 1.00 Former: 1.04 (0.90–1.19) Current: 1.43 (1.24–1.65)	Adjusted for age, alcohol, energy, protein, vitamin C and β carotene intake, estrogen and progesterone receptor, body mass index, oral contraceptive use, tumor type, stage, treatment, year of diagnosis, age at first birth and parity, menopausal status and postmenopausal hormone use.
					HR (95% CI)	
Hellmann et al. 2010 (12)	528 women with breast cancer, participating in the Copenhagen City Heart Study (CCHS). Age at diagnosis ranged from 33.1 to 95.4, with a median of 66.9.	Self-administered questionaire and clinical examination	Median of 7.8 years (ranging from 0.04–29.2)	Never Smokers: 48 Former Smokers: 34 Current Smokers: 96	Never: 1.00 Former: 0.98 (0.77–1.24) Current: 1.07 (0.94–1.23)	Adjusted for alcohol, physical activity, BMI, hormonereplacement therapy, age, disease stage, menopausal status, parity, education, and adjuvant treatment.
Warren et al. 2012 (13)	882 women with breast cancer among 5,185 cancer patients who received treatment at the Roswell ParkCancer Institute. Mean age at diagnosis was 55.7.	Completed a questionnaire within 1 month of cancer diagnosis	Follow-up ranged from 12 to 27.7 years.	Never Smokers: 480 Former Smokers: 220 Current Smokers: 143	Current vs. Former: 1.69 (1.16, 2.45) Current vs. never: 1.73 (1.28–2.33)	Adjusted for disease site, sex, age, stage (local, regional, distant), race, date of diagnosis, BMI at diagnosis, total pack-years of smoking.

First author, year (reference no)	Population	Assessment of smoking	Length of follow-up from smoking assessment till death or loss to follow-up	No. of breast cancer deaths	Main results	Adjustments
Barnett et al. 2008 (11)	4,560 women with invasive breast cancer who hadtaken part in the population-based Studies of Epidemiology and Risk Factors in Cancer Heredity (SEARCH) breast cancer study. 2,318 women were never smokers, 1,206 were Former smokers and 902 were current smokers.	Completed a self-administered questionnaire	Median of 6.82 years (ranging from 0.47–10)	Never Smokers: 308 Former Smokers: 156 Current Smokers: 134	Never: 1.00 Former: 1.01 (0.83–1.23) Current: 1.11 (0.89–1.41)	Adjusted for stage, grade, age at diagnosis, BMI, alcohol intake, recency of pregnancy, ER status,
This study	2265 women from the Life after Cancer Epidemiology (LACE) cohort, diagnosed with breast cancer between 1997 and 2000. 893 women were Former smokers, 173 women were current smokers, and 1199 women were never smokers. Mean age at enrollment was 57 years (SD=13.2 years; range 21–79 years).	Reported in questionnaire	Median follow-up was 9 years (SD=1.5 years; range 1–11 years).	Never Smokers: 72 Former Smokers: 76 Current Smokers: 16	Never: 1.00 Former: 1.24 (0.94,1.64) Current: 2.01 (1.27,3.18)	Physical activity, BMI, hormone replacement therapy, age, disease stage, menopausal status, parity, education, and adjuvant treatment.