OXFORD

JNCI Cancer Spectrum (2017) 1(1): pkx001

doi: 10.1093/jncics/pkx001
First published online September 21, 2017
Article

ARTICLE

Postdiagnosis Changes in Cigarette Smoking and Survival Following Breast Cancer

Humberto Parada Jr., Patrick T. Bradshaw, Susan E. Steck, Lawrence S. Engel, Kathleen Conway, Susan L. Teitelbaum, Alfred I. Neugut, Regina M. Santella, Marilie D. Gammon

Affiliations of authors: Department of Epidemiology, University of North Carolina at Chapel Hill, Chapel Hill, NC (HPJr, LSE, KC, MDG); Division of Epidemiology, School of Public Health, University of California, Berkeley, Berkeley, CA (PTB); Department of Epidemiology and Biostatistics, University of South Carolina, Columbia, SC (SES); Department of Preventive Medicine, Icahn School of Medicine at Mt. Sinai, New York, NY (SLT); Department of Epidemiology (AIN), Department of Medicine (AIN), and Department of Environmental Health Sciences (RMS), Columbia University, New York, NY.

Correspondence to: Humberto Parada, MPH, PhD, Department of Epidemiology, UNC Chapel Hill, 2101 McGavran-Greenberg Hall, CB #7435, Chapel Hill, NC 27599-7435 (e-mail: hparada@live.unc.edu).

Abstract

Background: The purpose of this study was to examine whether at-diagnosis smoking and postdiagnosis changes in smoking within five years after breast cancer were associated with long-term all-cause and breast cancer-specific mortality.
Methods: A population-based cohort of 1508 women diagnosed with first primary in situ or invasive breast cancer in 1996 to 1997 were interviewed shortly after diagnosis and again approximately five years later to assess smoking history. Participants were followed for vital status through December 31, 2014. After 18+ years of follow-up, 597 deaths were identified, 237 of which were breast cancer related. Multivariable Cox regression was used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs).
Results: Compared with never smokers, risk of all-cause mortality was elevated among the 19% of at-diagnosis smokers (HR = 1.69, 95% CI = 1.36 to 2.11), those who smoked 20 or more cigarettes per day (HR = 1.85, 95% CI = 1.42 to 2.40), women who had smoked for 30 or more years (HR = 1.62, 95% CI = 1.28 to 2.05), and women who had smoked 30 or more pack-years (HR = 1.82, 95% CI = 1.39 to 2.37). Risk of all-cause mortality was further increased among the 8% of women who were at-/post-diagnosis smokers (HR = 2.30, 95% CI = 1.56 to 3.39) but was attenuated among the 11% women who quit smoking after diagnosis (HR = 1.83, 95% CI = 1.32 to 2.52). Compared with never smokers, breast cancer–specific mortality risk was elevated 60% (HR = 1.60, 95% CI = 0.79 to 3.23) among at-/postdiagnosis current smokers, but the confidence interval included the null value and elevated 175% (HR = 2.75, 95% CI = 1.26 to 5.99) when we considered postdiagnosis cumulative pack-years.
Conclusions: Smoking negatively impacts long-term survival after breast cancer. Postdiagnosis cessation of smoking may reduce the risk of all-cause mortality. Breast cancer survivors may benefit from aggressive smoking cessation programs starting as early as the time of diagnosis.

Breast cancer is a serious public health problem in the United States, with more than 250 000 new breast cancer cases expected in 2017 (1). Although there have been vast improvements in breast cancer treatment over the last few decades (2) and breast cancer survival rates are high, estimated at 90% at five years after diagnosis, approximately 40 000 women will die from breast cancer in 2017 (1). This makes breast cancer the second leading cause of cancer-related death among women (1). The high incidence of breast cancer together with the high rate of survival contribute to an estimated 3.1 million breast cancer survivors (3).

After breast cancer diagnosis, survivors may be motivated to make behavioral and lifestyle changes if they believe it will help

Received: April 13, 2017; **Revised:** June 14, 2017; **Accepted:** July 6, 2017

improve prognosis, quality of life, and survival (4). For the 10% to 20% of women who are smokers at the time of breast cancer diagnosis (5,6), smoking cessation is one important behavioral change that may improve survival after breast cancer. Cigarettes are known to contain more than 7000 chemicals, including 69 known carcinogens such as benzene, arsenic, formaldehyde, vinyl chloride, N-nitrosamines, and polycyclic aromatic hydrocarbons (PAHs) (7). Therefore, it is not surprising that the association between smoking and breast cancer incidence has been extensively studied; at least 130 epidemiologic studies have examined this association, yet there is no scientific consensus (8). In addition to differences in study design and exposure assessment, the conflicting results may in part be explained by both the carcinogenic and estrogenic effects of cigarette smoke constituents on breast epithelial cells (9,10) and the anti-estrogenic effects of smoking on menstrual function (11,12). In their meta-analysis of more than 991 100 women from 15 cohort studies, Gaudet and colleagues reported a 12% increase in breast cancer incidence, which was further elevated among women who initiated smoking before a first birth and among women who developed estrogen receptor–positive (ER+) tumors (8). The few studies of smoking at the time of diagnosis and survival after breast cancer conducted to date consistently report a positive association between smoking and breast cancer–specific mortality (6,13–23). However, to date only one study (24) has prospectively considered the impact of postdiagnosis changes in smoking on survival.

This current study aimed to examine whether smoking at the time of diagnosis and changes in smoking within five years after diagnosis were associated with long-term all-cause and breast cancer mortality among a population-based sample of women diagnosed with first primary breast cancer.

Methods

We used resources from the Long Island Breast Cancer Study Project (LIBCSP), a population-based study of newly diagnosed breast cancer cases who were residents of Nassau and Suffolk counties on Long Island, New York, at the time of diagnosis. Details of the LIBCSP design have been published previously (25,26). Institutional review board approval was obtained from all participating institutions and in accordance with an assurance filed with and approved by the US Department of Health and Human Services.

Study Population

English-speaking women with a first primary diagnosis of in situ or invasive breast cancer were identified for inclusion using rapid-case ascertainment via active daily or weekly contact with local hospitals and confirmed by a physician and medical records. Additional eligibility criteria included being older than age 20 years and a resident of Nassau or Suffolk county on Long Island, New York, at the time of diagnosis between August 1, 1996, and July 31, 1997. The study reported here includes the 1508 case women who were interviewed at baseline, on average within three months of diagnosis (mean = 3.19 months). These women were primarily white (94%), with a mean age of 59 years (range = 25–98 years), and postmenopausal (68%) at diagnosis (Table 1).

Of the 1508 women who provided signed informed consent and completed the 100-minute, in-home, interviewer-administered, structured baseline questionnaire, 1414 agreed to continued contact. Approximately five years after the initial diagnosis of breast cancer, these 1414 women were recontacted for the follow-up interview. Informed consent was obtained by telephone from 1120 of the 1414 women (ie, 143 refused by mail or telephone, no proxy was identified for 96 women who were not alive at follow-up, and 55 could not be located). Of the 1120 consenting women, 65 were only able to provide limited information and 22 were refusals after consent and were therefore excluded. A 45-minute interviewer-administered, structured questionnaire that assessed information similar to that obtained at the time of diagnosis but regarding the time period since the initial diagnosis of breast cancer was completed by telephone by 1033 (68.5%) women, on average 5.48 years after diagnosis (range = 4.39–7.34 years) (27).

Smoking Assessment

Smoking history, including smoking status, intensity, and duration, was determined via interviewer-administered questionnaires at baseline and at five-year follow-up (28). Smokers were defined as women who smoked at least one cigarette a day for six months or longer. Smoking status at baseline was defined as never, former, and current smoking in the year before diagnosis, and smoking status at the follow-up was similarly defined, but in the year before the follow-up interview. Intensity of smoking, or the number of cigarettes smoked per day, was categorized as fewer than 20 cigarettes per day and 20 or more cigarettes per day. Duration of smoking, or the total number of years of smoking excluding any time periods the women reported having not smoked, was categorized as less than 15 years, 15 to less than 30 years, and 30 or more years of smoking. Cigarette pack-years was calculated by multiplying the average number of cigarette packs smoked per day and the total number of years of smoking and was categorized as less than 15 pack-years, 15 to less than 30 pack-years, and 30 or more pack-years. At baseline, smoking cessation (recency) among former smokers was categorized as less than five years, five to less than 10 years, and 10 or more years. In the analyses of postdiagnosis changes in smoking, each combination of at-diagnosis/postdiagnosis smoking was examined (ie, never/never smokers, former/former smokers, current/former smokers, and current/current smokers).

Covariate Assessment

Covariates were assessed by interviewer-administered questionnaire. Potential confounders were selected using directed acyclic graphs (29) and putative relationships based on previous studies of smoking and breast cancer survival. These covariates included age at diagnosis (years), total annual household income (<$15 000–$24 999, $25 000–$49 999, and ≥$50 000), education (<high school or high school graduate, some college or college graduate, and postcollege), marital status (married or living as married vs not married, divorced, or widowed), body mass index (continuous, kg/m^2), at-diagnosis recreational physical activity (never, former, and current physical activity of least one hour per week for three months or more), and at-diagnosis intake of alcoholic beverages such as beer, wine, or liquor (never, former, and current intake at least once a month for six months or more).

Estrogen receptor status and nodal involvement were determined by medical record review, and tumor size was obtained from the New York State Cancer Registry. At baseline, women were interviewed after surgery but before initiation of most

Table 1. Distribution of selected at-diagnosis participant and disease characteristics of the LIBCSP women diagnosed with breast cancer in 1996–1997 (n = 1508), overall and by at-diagnosis smoking status*

		At-diagnosis smoking status†		
At-diagnosis characteristic	Total (n = 1508) No. (%)	Never smokers (n = 674) No. (%)	Former smokers (n = 544) No. (%)	Current smokers (n = 290) No. (%)
Age at diagnosis, y				
<50	407 (27.0)	192 (28.5)	122 (22.4)	93 (32.1)
50–64	582 (38.6)	230 (34.1)	219 (40.3)	133 (45.9)
≥65	519 (34.4)	252 (37.4)	203 (37.3)	64 (22.1)
Mean (SD)	58.8 (12.7)	59.4 (13.6)	59.9 (11.9)	55.5 (11.3)
Menopausal status				
Premenopausal	472 (31.9)	216 (32.6)	146 (27.3)	110 (39.0)
Postmenopausal	1006 (68.1)	446 (67.4)	388 (72.7)	172 (61.0)
Income				
<$15 000–$24 999	286 (19.0)	154 (22.9)	78 (14.4)	54 (18.7)
$25 000–$49 999	488 (32.4)	205 (30.5)	189 (34.9)	94 (32.5)
≥$50 000	730 (48.5)	314 (46.7)	275 (50.7)	141 (48.8)
Education				
<HS/HS graduate	721 (48.0)	334 (49.7)	240 (44.3)	147 (51.0)
Some college/college graduate	551 (36.7)	223 (33.2)	214 (39.5)	114 (39.6)
Postcollege	230 (15.3)	115 (17.1)	88 (16.2)	27 (9.4)
Marital status				
Married or living as married	1029 (68.3)	459 (68.1)	388 (71.3)	182 (63.0)
Not married	478 (31.7)	215 (31.9)	156 (28.7)	107 (37.0)
BMI at diagnosis, kg/m^2				
<25.0	683 (45.8)	284 (42.6)	237 (44.1)	162 (56.3)
25.0–29.9	476 (31.9)	227 (34.1)	174 (32.4)	75 (26.0)
≥30.0	332 (22.3)	155 (23.3)	126 (23.5)	51 (17.7)
Mean (SD)	26.6 (5.7)	26.9 (5.8)	26.9 (5.6)	25.5 (5.5)
Physical activity‡				
Never	334 (22.5)	157 (23.6)	109 (20.3)	68 (23.9)
Former	253 (17.0)	102 (15.4)	97 (18.0)	54 (18.9)
Current	900 (60.5)	405 (61.0)	332 (61.7)	163 (57.2)
Alcohol intake§				
Never	588 (39.0)	329 (48.8)	163 (30.0)	96 (33.1)
Former	212 (14.1)	76 (11.3)	90 (16.6)	46 (15.9)
Current	707 (46.9)	269 (39.9)	290 (53.4)	148 (51.0)
Stage				
Invasive	1273 (84.4)	567 (84.1)	454 (83.5)	252 (86.9)
In situ	235 (15.6)	107 (15.9)	90 (16.5)	38 (13.1)
Nodal involvement				
No	213 (25.5)	89 (24.7)	86 (27.4)	38 (23.6)
Yes	622 (74.5)	271 (75.3)	228 (72.6)	123 (76.4)
Tumor size, cm				
≤2.0	622 (75.5)	258 (72.1)	247 (79.2)	117 (76.0)
>2.0	202 (24.5)	100 (27.9)	65 (20.8)	37 (24.0)
Mean (SD)	1.7 (1.6)	1.8 (1.6)	1.6 (1.5)	1.8 (1.8)
Estrogen receptor status				
Negative	264 (26.7)	123 (28.0)	88 (25.1)	53 (26.6)
Positive	726 (73.3)	317 (72.1)	263 (74.9)	146 (73.4)
Treatment received				
Radiation	625 (60.9)	261 (57.1)	235 (63.5)	129 (64.8)
Chemotherapy	423 (41.4)	197 (43.4)	146 (39.6)	80 (40.2)
Hormone therapy	616 (61.1)	280 (62.5)	228 (63.0)	108 (54.3)

*Long Island Breast Cancer Study Project participants diagnosed with breast cancer between August 1, 1996, and July 31, 1997, followed up for vital status through December 31, 2014. BMI = body mass index; HS = high school; LIBCSP = Long Island Breast Cancer Study Project.

†At-diagnosis smoking status was defined as never, former, and current cigarette smoking in the year prior to breast cancer diagnosis.

‡At-diagnosis recreational physical activity was defined as never, former, and current physical activity of least one hour per week for three months or more.

§At-diagnosis intake of alcoholic beverages was defined as never, former, and current intake of alcoholic beverages such as beer, wine, or liquor at least once a month for six months or more.

other components of the first course of treatment for the first primary breast cancer. Therefore, treatment received (radiation therapy, chemotherapy, or hormone therapy) was assessed by self-report at the follow-up questionnaire, which showed high agreement with medical record data (radiation therapy $\kappa = 0.97$, chemotherapy $\kappa = 0.96$, hormone therapy $\kappa = 0.92$) (30) but was more complete.

Outcome Assessment

We used the National Death Index (NDI) (31) to ascertain date of death and cause of death. Breast cancer–related deaths were identified using International Statistical Classification of Diseases 9 (174.9) and 10 (C-50.9) codes for deaths occurring before and after 1999, respectively, listed on the death certificate. Follow-up for mortality occurred from the date of diagnosis in 1996 to 1997 until December 31, 2014. The median duration of follow-up was 17.61 years (range = 0.23–18.41 years). Among the 1508 women, 597 deaths occurred by the end of follow-up at 18+ years, 237 of which were breast cancer related.

Statistical Analysis

We used multivariable Cox proportional hazards models to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for the associations between at-diagnosis as well as at-/postdiagnosis cigarette smoking and all-cause and breast cancer–specific mortality. The proportional hazards assumption was assessed by visual inspection of Kaplan-Meier curves and by testing exposure-by-time interactions in Cox models; no violations of the proportional hazards assumptions were observed. All analyses were done using the Kaplan-Meier and Cox Regression function in IBM SPSS Statistics version 22.0 (IBM Corp., Armonk, NY) and used never smokers as the referent group.

In the analyses of at-diagnosis smoking, survival time began at the date of breast cancer diagnosis and continued until the earlier of date of death or December 31, 2014. Age-adjusted and multivariable-adjusted models were fit for each of the exposures separately and for all-cause and breast cancer–specific mortality. The analyses of at-diagnosis smoking were not adjusted for disease and treatment characteristics, which occur and are ascertained after diagnosis and therefore do not meet the temporal condition necessary to be confounders. Furthermore, disease and treatment characteristics could be mediators if, for example, smoking influences the likelihood of estrogen receptor–positive breast cancer, which influences treatment and subsequent prognosis (8).

The analyses of postdiagnosis change in smoking were restricted to the 1339 women who survived at least five years after diagnosis. Accordingly, survival time began at the date of completion of the follow-up questionnaire to the date of death or December 31, 2014, if alive. After excluding an additional seven women who reported being former smokers before diagnosis and current smokers at the follow-up questionnaire, the analytic sample consisted of 1332 women. Of these, 377 (28%) were lost to follow-up. Because a complete case analysis when data are not missing completely at random is inefficient and can potentially lead to biased results (32), we employed multiple imputation to account for the missing data. Missing values were imputed using SPSS, which employs a fully conditional specification (FCS) algorithm (33). The FCS method is an iterative Markov Chain Monte Carlo procedure that sequentially imputes missing values for all covariates included starting from the first variable with missing values by specifying a linear regression or logistic regression model for each continuous or categorical variable, respectively. We used 25 imputations with 1000 iterations and included demographics (age at diagnosis, menopausal status, income, education, marital status, body mass index, physical activity, and alcohol intake), postdiagnosis smoking exposures (smoking status, number of cigarettes smoked per day at follow-up [minimum = 0], cumulative years of smoking [minimum = 0], and cumulative pack-years of smoking [minimum = 0]), disease characteristics (stage, tumor size, nodal status, estrogen receptor status), treatment (radiation therapy, chemotherapy, and hormone therapy), and the outcome (the event indicator and the Nelson-Aalen estimator of the cumulative hazard) (34). The analyses of postdiagnosis smoking were additionally adjusted for stage, tumor size, nodal status, ER status, and chemotherapy treatment. In this report, we present the results from the full case analysis; however, the results of the complete case analysis for the age-adjusted estimates are available in the Supplementary Material (Supplementary Table 1, available online).

Results

Prevalence of Smoking Among Women With Breast Cancer

Among the LIBCSP population-based sample of women diagnosed with first primary breast cancer in 1996 to 1997, 19% reported smoking within a year of their diagnosis About five years after diagnosis, 8% of women reported continued smoking and 11% reported that they had quit smoking since diagnosis.

At-Diagnosis Smoking and Survival After Breast Cancer

Compared with never smokers, current smoking at the time of breast cancer diagnosis was associated with a 69% increased hazard (HR = 1.69, 95% CI = 1.36 to 2.11) of all-cause mortality after covariate adjustment (Table 2). Risk of all-cause mortality was increased 50% for current smokers who smoked fewer than 20 cigarettes per day and 85% for current smokers who smoked 20 or more cigarettes per day (HR = 1.85, 95% CI = 1.42 to 2.40). Current smokers who had smoked for 15 to less than 30 years had a 107% increased risk, and women who smoked 30 or more years had a 62% increased risk of all-cause mortality (HR = 1.62, 95% CI = 1.28 to 2.05). All-cause mortality was also increased among former smokers and current smokers who had smoked 30 or more pack-years (HR = 1.82, 95% CI = 1.39 to 2.37). Additionally, risk of all-cause mortality was elevated among former smokers who had quit smoking within five years of diagnosis, but not among women who had quit smoking five or more years before diagnosis. At-diagnosis smoking was not associated with breast cancer–specific mortality.

At-/Postdiagnosis Smoking and Survival After Breast Cancer

Table 3 shows the results of the full case analyses utilizing the imputed data, and Supplementary Table 1 (available online) shows the results of the complete case analysis for the age-adjusted estimates. Overall, the results of both analyses are consistent. As shown in Table 3, the risk of all-cause mortality was elevated 130% among women who continued smoking after diagnosis as compared with never smokers, after covariate

Table 2. Cox regression hazard ratios and 95% confidence intervals for the association between at-diagnosis cigarette smoking and mortality in the LIBCSP women diagnosed with breast cancer in 1996–1997 (n = 1508)*

	All-cause mortality (No. of deaths = 597)				Breast cancer–specific mortality (No. of deaths = 237)			
At-diagnosis smoking	Deaths	Censored	Age-adjusted HR (95% CI)	Multivariable-adjusted† HR (95% CI)	Deaths	Censored	Age-adjusted HR (95% CI)	Multivariable-adjusted† HR (95% CI)
Never smokers‡	258	416	Referent	Referent	112	562	Referent	Referent
Cigarette smoking status								
Former smokers	206	338	0.98 (0.82 to 1.18)	1.01 (0.84 to 1.22)	74	470	0.81 (0.60 to 1.09)	0.82 (0.61 to 1.11)
Current smokers	133	157	1.69 (1.37 to 2.10)	1.69 (1.36 to 2.11)	51	239	1.14 (0.81 to 1.59)	1.08 (0.77 to 1.51)
Intensity of smoking, cigarettes/d								
Former smokers								
<20	93	416	0.80 (0.63 to 1.01)	0.86 (0.67 to 1.09)	35	255	0.70 (0.48 to 1.03)	0.72 (0.49 to 1.06)
≥20	109	138	1.21 (0.96 to 1.51)	1.18 (0.93 to 1.48)	39	208	0.96 (0.67 to 1.39)	0.97 (0.67 to 1.41)
Current smokers								
<20	53	73	1.47 (1.09 to 1.98)	1.50 (1.10 to 2.03)	23	103	1.15 (0.73 to 1.80)	1.10 (0.70 to 1.73)
≥20	80	83	1.90 (1.48 to 2.46)	1.85 (1.42 to 2.40)	28	135	1.13 (0.75 to 1.72)	1.06 (0.70 to 1.61)
Duration of smoking, y								
Former smokers								
<15	45	131	0.79 (0.58 to 1.09)	0.84 (0.61 to 1.17)	23	153	0.75 (0.48 to 1.18)	0.78 (0.49 to 1.24)
≥15–<30	61	123	0.90 (0.68 to 1.19)	0.94 (0.70 to 1.25)	20	164	0.65 (0.40 to 1.04)	0.65 (0.40 to 1.06)
≥30	100	84	1.17 (0.93 to 1.48)	1.17 (0.92 to 1.49)	31	153	1.04 (0.69 to 1.56)	1.04 (0.69 to 1.57)
Current smokers								
<15	5	6	1.72 (0.71 to 4.17)	1.57 (0.57 to 4.28)	<5	9	–	–
≥15–<30	21	48	2.09 (1.30 to 3.37)	2.07 (1.28 to 3.35)	15	54	1.39 (0.79 to 2.46)	1.32 (0.74 to 2.36)
≥30	106	103	1.62 (1.29 to 2.03)	1.62 (1.28 to 2.05)	34	175	1.05 (0.72 to 1.54)	0.99 (0.67 to 1.46)
Pack-years of smoking								
Former smokers								
<15	87	196	0.84 (0.66 to 1.07)	0.90 (0.70 to 1.15)	37	246	0.77 (0.53 to 1.11)	0.80 (0.55 to 1.17)
≥15–<30	30	70	0.74 (0.51 to 1.09)	0.73 (0.49 to 1.08)	11	89	0.61 (0.33 to 1.14)	0.61 (0.33 to 1.14)
≥30	83	63	1.39 (1.08 to 1.78)	1.36 (1.05 to 1.76)	26	120	1.14 (0.74 to 1.76)	1.16 (0.75 to 1.79)
Current smokers								
<15	27	47	1.50 (1.00 to 2.25)	1.58 (1.05 to 2.39)	13	61	1.10 (0.62 to 1.97)	1.18 (0.66 to 2.11)
≥15–<30	29	43	1.58 (1.07 to 2.34)	1.39 (0.94 to 2.06)	16	56	1.37 (0.81 to 2.33)	1.10 (0.65 to 1.89)
≥30	76	65	1.78 (1.38 to 2.30)	1.82 (1.39 to 2.37)	22	119	1.04 (0.66 to 1.64)	1.01 (0.63 to 1.60)
Smoking cessation recency, y								
Former smokers								
<5	29	31	1.92 (1.30 to 2.82)	1.97 (1.33 to 2.93)	12	48	1.43 (0.79 to 2.60)	1.46 (0.80 to 2.67)
≥5–<10	30	62	0.94 (0.64 to 1.37)	0.94 (0.64 to 1.37)	11	81	0.68 (0.37 to 1.27)	0.66 (0.35 to 1.22)
≥10	147	245	0.90 (0.74 to 1.11)	0.94 (0.76 to 1.16)	51	341	0.76 (0.55 to 1.06)	0.79 (0.56 to 1.10)
Current smokers	133	157	1.70 (1.38 to 2.11)	1.70 (1.36 to 2.12)	51	239	1.14 (0.82 to 1.59)	1.08 (0.77 to 1.52)

*Long Island Breast Cancer Study Project participants diagnosed with breast cancer between August 1, 1996, and July 31, 1997, followed up for vital status through December 31, 2014. CI = confidence interval; HR = hazard ratio; LIBCSP = Long Island Breast Cancer Study Project.
†Adjusted for age at diagnosis, body mass index, marital status, income, alcohol intake, and physical activity.
‡Never smokers were the referent group in all analyses.

adjustment (HR = 2.30, 95% CI = 1.56 to 3.39). However, risk of all-cause mortality was attenuated among women who quit smoking after diagnosis (HR = 1.83, 95% CI = 1.32 to 2.52). This pattern of association for women who quit smoking after diagnosis and women who continued smoking was consistent across high smoking intensity and high cumulative duration of smoking. However, women with 30 or more cumulative pack-years of smoking who quit after diagnosis had a slightly greater risk of mortality as compared with women who did not quit after diagnosis. These findings were similar among women with invasive breast cancer only (Supplementary Table 2) and stronger among women with ER+ breast cancer (Supplementary Table 3), though data were sparse.

At-/postdiagnosis smoking status, intensity, and duration were not statistically significantly associated with breast cancer–specific mortality. However, we noted elevations in the breast cancer–specific mortality rate among women who continued smoking after diagnosis (HR = 1.60, 95% CI = 0.79 to 3.23) and among women who continued smoking fewer than 20 cigarettes per day. Risk of breast cancer–specific mortality was elevated among women who continued smoking and who had smoked less than 30 cumulative pack-years (HR = 2.75, 95% CI = 1.26 to 5.99). Due to small numbers, we were unable to estimate the risk of mortality among women who continued smoking and who had smoked 30 or more cumulative pack-years.

Discussion

In this population-based study of women diagnosed with first primary breast cancer, at-diagnosis smoking was associated

Table 3. Cox regression hazard ratios and 95% confidence intervals for the association between at-/postdiagnosis cigarette smoking and mortality in the LIBCSP women diagnosed with breast cancer in 1996–1997 (n = 1332)*

	All-cause mortality (No. of deaths = 426)				Breast cancer–specific mortality (No. of deaths = 125)			
At-/postdiagnosis smoking	Deaths	Censored	Age-adjusted HR (95% CI)	Multivariable-adjusted† HR (95% CI)	Deaths	Censored	Age-adjusted HR (95% CI)	Multivariable-adjusted† HR (95% CI)
Never/never smokers‡	185	416	Referent	Referent	59	542	Referent	Referent
Cigarette smoking status								
Former/former smokers	144	333	0.96 (0.86 to 1.07)	1.00 (0.80 to 1.25)	40	437	0.84 (0.68 to 1.03)	0.86 (0.57 to 1.30)
Current/former smokers	55	90	1.73 (1.27 to 2.36)	1.83 (1.32 to 2.52)	12	133	0.92 (0.47 to 1.80)	1.01 (0.51 to 1.98)
Current/current smokers	42	67	2.25 (1.54 to 3.28)	2.30 (1.56 to 3.39)	14	95	1.48 (0.75 to 2.90)	1.60 (0.79 to 3.23)
Intensity of smoking§, cigarettes/d								
Former/former smokers								
<20	79	198	0.89 (0.67 to 1.18)	0.91 (0.69 to 1.22)	19	258	0.73 (0.43 to 1.24)	0.73 (0.43 to 1.26)
≥20	65	135	1.05 (0.78 to 1.42)	1.11 (0.82 to 1.51)	21	179	0.97 (0.57 to 1.66)	1.03 (0.60 to 1.78)
Current/former smokers								
<20	35	70	1.70 (1.17 to 2.49)	1.79 (1.21 to 2.66)	10	95	0.94 (0.41 to 2.13)	1.00 (0.44 to 2.29)
≥20	20	20	1.79 (0.89 to 3.60)	1.86 (0.92 to 3.88)	<5	38	–	–
Current/current smokers								
<20	22	39	1.80 (1.06 to 3.05)	1.85 (1.09 to 3.16)	11	50	1.93 (0.93 to 4.00)	1.98 (0.94 to 4.17)
≥20	20	28	2.93 (1.77 to 4.85)	2.95 (1.77 to 4.93)	<5	45	–	–
Duration of smoking, y								
Former/former smokers								
<30	82	241	0.91 (0.70 to 1.19)	0.94 (0.71 to 1.23)	23	300	0.75 (0.46 to 1.24)	0.74 (0.45 to 1.23)
≥30	62	92	1.03 (0.76 to 1.39)	1.10 (0.80 to 1.50)	17	137	1.00 (0.54 to 1.86)	1.15 (0.61 to 2.16)
Current/former smokers								
<30	31	47	1.76 (1.12 to 2.77)	1.77 (1.11 to 2.82)	5	73	0.72 (0.20 to 2.55)	0.79 (0.22 to 2.83)
≥30	24	43	1.71 (1.15 to 2.55)	1.87 (1.24 to 2.83)	7	60	1.07 (0.48 to 2.41)	1.17 (0.51 to 2.67)
Current/current smokers								
<30	<5	12	–	–	<5	12	–	–
≥30	38	55	2.17 (1.47 to 3.20)	2.23 (1.49 to 3.33)	10	83	1.27 (0.58 to 2.75)	1.36 (0.61 to 3.03)
Pack-years of smoking								
Former/former smokers								
<30	90	260	0.87 (0.67 to 1.13)	0.90 (0.69 to 1.18)	24	326	0.71 (0.44 to 1.15)	0.71 (0.44 to 1.17)
≥30	54	73	1.15 (0.83 to 1.59)	1.23 (0.88 to 1.72)	16	111	1.17 (0.64 to 2.16)	1.28 (0.69 to 2.38)
Current/former smokers								
<30	33	66	1.51 (1.01 to 2.27)	1.56 (1.03 to 2.39)	7	91	0.78 (0.33 to 1.86)	0.83 (0.35 to 2.01)
≥30	22	24	2.15 (1.32 to 3.50)	2.36 (1.43 to 3.89)	5	42	1.18 (0.41 to 3.42)	1.35 (0.46 to 3.99)
Current/current smokers								
<30	14	27	2.43 (1.32 to 4.46)	2.65 (1.45 to 4.84)	9	32	2.44 (1.14 to 5.21)	2.75 (1.26 to 5.99)
≥30	28	40	2.14 (1.35 to 3.40)	2.12 (1.32 to 3.43)	<5	63	–	–

*Long Island Breast Cancer Study Project participants diagnosed with breast cancer between August 1, 1996, and July 31, 1997, followed up for vital status through December 31, 2014. Missing data analyses exclude women who died within five years of breast cancer diagnosis (n = 169) and women who reported post-, but not at-, diagnosis smoking (n = 7). CI = confidence interval; HR = hazard ratio; LIBCSP = Long Island Breast Cancer Study Project.
†Adjusted for age at diagnosis, body mass index, marital status, income, alcohol intake, physical activity, stage, tumor size, nodal status, estrogen receptor status, and chemotherapy treatment.
‡Never/never smokers were the referent group in all analyses.
§Intensity of smoking was based on most recent smoking status.

with a 69% increase in the risk of long-term all-cause, but not breast cancer–specific, mortality. Among women who continued smoking after breast cancer, the risk of all-cause mortality was elevated 130%. However, among the approximately 20% of women who quit smoking after diagnosis, the elevated mortality risk was attenuated. Additionally, among women who continued smoking, less than 30 cumulative pack-years of smoking was associated with more than a twofold increase in the risk of breast cancer–specific mortality.

While the carcinogenic constituents in tobacco smoke have been hypothesized to increase the risk of incident breast cancer (8), little is known about how these chemicals may increase risk of recurrence and subsequent mortality. PAHs, which are present in tobacco smoke, for example, can exert estrogenic as well as anti-estrogenic effects (35) and may be important in influencing survival in women with hormonally sensitive breast tumors. Our findings of an association between at-diagnosis smoking and all-cause, but not breast cancer–specific, mortality are inconsistent with most studies conducted to date, which report approximately a 30% increased risk (6); however, the confidence interval, which ranged from 0.77 to 1.51, suggests that these data may in fact be consistent. Among former smokers, we observed a suggestive inverse association with breast cancer mortality, which is consistent with at least two prior studies (36,37). One possible explanation for this finding is that successful quitters may also adopt healthier lifestyle behaviors, including an increase in the use of routine clinical preventive services such as mammographic screening (38).

Studies examining smoking and mortality after breast cancer have primarily examined at-diagnosis smoking only (6). However, one recently published study (24) prospectively evaluated changes in smoking status approximately six years after breast cancer diagnosis, which is an approach similar to that used in the study reported here. Although there were several differences in the study population in the study by Passarelli and colleagues, including the exclusion of women with in situ disease and women with stage IV disease in their study, Passarelli and colleagues reported similar estimates that were slightly larger in magnitude than those reported here for women who continued smoking after breast cancer for all-cause (HR = 2.57, 95% CI = 2.06 to 3.21, vs 2.30, 95% CI = 1.56 to 3.39, respectively) and breast cancer–specific (HR = 1.73, 95% CI = 1.13 to 2.60, vs HR = 1.60, 95% CI = 0.79 to 3.23, respectively) mortality. These differences may arise from different approaches in addressing missing data. The response rate for the completion of our follow-up assessment was approximately 70%, which is better than the 40% in the study by Passarelli et al., and we addressed the missing data due to potential biases that may arise from a complete case analysis only (32).

Similar to prior studies of smoking and mortality among breast cancer survivors, our study has several limitations. First, our assessments of smoking relied on self-report; however, smoking history has been shown to be reliably recalled and self-reported (39). Although women with newly diagnosed breast cancer may misreport their smoking status, our prevalence estimates for at-diagnosis (19%) (6) and postdiagnosis smoking (8%) are consistent with prior studies (5,40). Second, although our study shows that smoking may adversely impact survival, we can only hypothesize about the underlying biological mechanisms given the complex nature of tobacco smoke. It is possible that our findings are confounded by changes in other behaviors such as alcohol intake after diagnosis, which we were unable to consider in the same models due to insufficient power; however, most studies of alcohol intake and breast cancer mortality have been null (41). We also lacked information on specific stage at diagnosis, an important determinant of survival, as well as the reasons women quit smoking after diagnosis, both of which could potentially confound the associations with postdiagnosis smoking reported here. Third, the low number of breast cancer–specific deaths, in particular for the analyses examining postdiagnosis changes in smoking, resulted in estimates that were imprecise and may be one reason for any discrepancies in our results with previous studies. Fourth, we did not consider causes of death other than breast cancer, and thus the results from breast cancer–specific analysis do not necessarily translate into the absolute risk of this outcome (42). However, our approach does accurately estimate the relative hazard (rate) of breast cancer–specific death and thus addresses how death from breast cancer is associated with smoking (42,43). This is an etiologically relevant question given the potential of cigarette smoke chemicals to disrupt the endocrine system. Last, while our prospective study design allowed us to assess changes in smoking status several years after breast cancer, a proportion of women were lost to follow-up and thus did not complete the follow-up assessment; however, we addressed the missing data using multiple imputation, resulting in valid statistical inferences that properly reflect the uncertainty due to missing values (44).

The results of our study show that smoking negatively impacts long-term survival after breast cancer. These findings support clinical opportunities for promoting smoking cessation programs targeted to women newly diagnosed with breast cancer and continued throughout the survivorship continuum in order to reduce the risk of mortality associated with continued smoking. Emphasis should also be placed on systematically assessing the impact of smoking history, smoking status, and postdiagnosis changes in smoking on outcomes in clinical trials, which often fail to account for this important exposure (45).

Funding

This study was funded by the National Cancer Institute and the National Institute of Environmental Health Sciences (grant numbers UO1 CA/ES66572, UO1 CA66572, T32 ES007018, R25 CA057726).

Notes

H. Parada declares that he has no conflict of interest. P. T. Bradshaw declares that he has no conflict of interest. S. E. Steck declares that she has no conflict of interest. L. S. Engel declares that he has no conflict of interest. K. Conway declares that she has no conflict of interest. S. L. Teitelbaum declares that she has no conflict of interest. A. I. Neugut declares that he has no conflict of interest. R. M. Santella declares that she has no conflict of interest. M. D. Gammon declares that she has no conflict of interest.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent was obtained from all individual participants included in the study.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2017. *CA Cancer J Clin.* 2017;67(1):7–30.
2. Sledge GW, Mamounas EP, Hortobagyi GN, Burstein HJ, Goodwin PJ, Wolff AC. Past, present, and future challenges in breast cancer treatment. *J Clin Oncol.* 2014;32(19):1979–1986.
3. American Cancer Society. *Cancer Treatment and Survivorship Facts and Figures 2014-2015.* Atlanta, GA: ACS; 2014.
4. McBride CM, Ostroff JS. Teachable moments for promoting smoking cessation: The context of cancer care and survivorship. *Cancer Control.* 2003;10(4):325–333.
5. Westmaas JL, Newton CC, Stevens VL, Flanders WD, Gapstur SM, Jacobs EJ. Does a recent cancer diagnosis predict smoking cessation? An analysis from a large prospective US cohort. *J Clin Oncol.* 2015;33(15):1647–1652.
6. Bérubé S, Lemieux J, Moore L, Maunsell E, Brisson J. Smoking at time of diagnosis and breast cancer-specific survival: New findings and systematic review with meta-analysis. *Breast Cancer Res.* 2014;16(2):R42.
7. International Agency for Research on Cancer. *IARC Monographs on Evaluation of Carcinogenic Risks to Humans: Tobacco Smoke and Involuntary Smoking.* Lyon, France: IARC; 2004.
8. Gaudet MM, Gapstur SM, Sun J, Diver WR, Hannan LM, Thun MJ. Active smoking and breast cancer risk: Original cohort data and meta-analysis. *J Natl Cancer Inst.* 2013;105(8):515–525.
9. Meek MD, Finch GL. Diluted mainstream cigarette smoke condensates activate estrogen receptor and aryl hydrocarbon receptor-mediated gene transcription. *Environ Res.* 1999;80(1):9–17.
10. Rodgman A, Smith CJ, Perfetti TA. The composition of cigarette smoke: A retrospective, with emphasis on polycyclic components. *Hum Exp Toxicol.* 2000;19(10):573–595.
11. Baron JA, La Vecchia C, Levi F. The antiestrogenic effect of cigarette smoking in women. *Am J Obstet Gynecol.* 1990;162(2):502–514.
12. Windham GC, Elkin EP, Swan SH, Waller KO, Fenster L. Cigarette smoking and effects on menstrual function. *Obstet Gynecol.* 1999;93(1):59–65.

13. Braithwaite D, Izano M, Moore DH, et al. Smoking and survival after breast cancer diagnosis: A prospective observational study and systematic review. *Breast Cancer Res Treat.* 2012;136(2):521–533.
14. Warren GW, Kasza KA, Reid ME, Cummings KM, Marshall JR. Smoking at diagnosis and survival in cancer patients. *Int J cancer.* 2012;132(2):401–410.
15. Hellmann SS, Thygesen LC, Tolstrup JS, Grønbæk M. Modifiable risk factors and survival in women diagnosed with primary breast cancer: Results from a prospective cohort study. *Eur J Cancer Prev.* 2010;19(5):366–373.
16. Holmes MD, Murin S, Chen WY, Kroenke CH, Spiegelman D, Colditz GA. Smoking and survival after breast cancer diagnosis. *Int J Cancer.* 2007;120(12): 2672–2677.
17. Manjer J. Survival of women with breast cancer in relation to smoking. *Eur J Surg.* 2000;166(11):852–858.
18. Holmes MD, Stampfer MJ, Colditz GA, Rosner B, Hunter DJ, Willett WC. Dietary factors and the survival of women with breast carcinoma. *Cancer.* 1999;86(5):826–835.
19. Tominaga K, Andow J, Koyama Y, et al. Family environment, hobbies and habits as psychosocial predictors of survival for surgically treated patients with breast cancer. *Jpn J Clin Oncol.* 1998;28(1):36–41.
20. Yu GP, Ostroff JS, Zhang ZF, Tang J, Schantz SP. Smoking history and cancer patient survival: A hospital cancer registry study. *Cancer Detect Prev.* 1997; 21(6):497–509.
21. Calle EE, Miracle-McMahill HL, Thun MJ, Heath CW Jr. Cigarette smoking and risk of fatal breast cancer. *Am J Epidemiol.* 1994;139(10):1001–1007.
22. Pierce JP, Patterson RE, Senger CM, et al. Lifetime cigarette smoking and breast cancer prognosis in the After Breast Cancer Pooling Project. *J Natl Cancer Inst.* 2014;106(1):1–8.
23. Dal Maso L, Zucchetto A, Talamini R, et al. Effect of obesity and other lifestyle factors on mortality in women with breast cancer. *Int J Cancer.* 2008;123(9): 2188–2194.
24. Passarelli MN, Newcomb PA, Hampton JM, et al. Cigarette smoking before and after breast cancer diagnosis: Mortality from breast cancer and smoking-related diseases. *J Clin Oncol.* 2016;34:1–8.
25. Gammon MD, Neugut AI, Santella RM, et al. The Long Island Breast Cancer Study Project: Description of a multi-institutional collaboration to identify environmental risk factors for breast cancer. *Breast Cancer Res Treat.* 2002; 74(3):235–254.
26. Gammon MD, Wolff MS, Neugut AI, et al. Environmental toxins and breast cancer on Long Island. II. Organochlorine compound levels in blood. *Cancer Epidemiol Biomarkers Prev.* 2002;11(8):686–697.
27. Bradshaw PT, Ibrahim JG, Stevens J, et al. Postdiagnosis change in bodyweight and survival after breast cancer diagnosis. *Epidemiology.* 2012;23(2): 320–327.
28. Gammon MD, Eng SM, Teitelbaum SL, et al. Environmental tobacco smoke and breast cancer incidence. *Environ Res.* 2004;96(2):176–185.
29. Greenland S, Pearl J, Robins JM. Causal diagrams for epidemiologic research. *Epidemiology.* 1999;10(1):37–48.
30. Cleveland RJ, Eng SM, Abrahamson PE, et al. Weight gain prior to diagnosis and survival from breast cancer. *Cancer Epidemiol Biomarkers Prev.* 2007;16(9): 1803–1811.
31. Centers for Disease Control and Prevention. National Death Index. 2014. http://www.cdc.gov/nchs/ndi.htm. Accessed June 29, 2016.
32. Ibrahim JG, Chu H, Chen M-H. Missing data in clinical studies: Issues and methods. *J Clin Oncol.* 2012;30(26):3297–3303.
33. van Buuren S. Multiple imputation of discrete and continuous data by fully conditional specification. *Stat Methods Med Res.* 2007;16(3):219–242.
34. White IR, Royston P. Imputing missing covariate values for the Cox model. *Stat Med.* 2009;28(15):1982–1998.
35. Santodonato J. Review of the estrogenic and antiestrogenic activity of polycyclic aromatic hydrocarbons: Relationship to carcinogenicity. *Chemosphere.* 1997;34(4):835–848.
36. Kakugawa Y, Kawai M, Nishino Y, et al. Smoking and survival after breast cancer diagnosis in Japanese women: A prospective cohort study. *Cancer Sci.* 2015;106(8):1066–1074.
37. Fentiman IS, Allen DS, Hamed H. Smoking and prognosis in women with breast cancer. *Int J Clin Pract.* 2005;59(9):1051–1054.
38. Caplan LS, Mandelson MT, Anderson LA. Validity of self-reported mammography: Examining recall and covariates among older women in a health maintenance organization. *Am J Epidemiol.* 2003;157(3):267–272.
39. Krall EA, Valadian I, Dwyer JT, Gardner J. Accuracy of recalled smoking data. *Am J Public Health.* 1989;79(2):200–202.
40. Mayer DK, Carlson J. Smoking patterns in cancer survivors. *Nicotine Tob Res.* 2011;13(1):34–40.
41. Gou Y-J, Xie D-X, Yang K-H, et al. Alcohol consumption and breast cancer survival: A meta-analysis of cohort studies. *Asian Pac J Cancer Prev.* 2013;14(8):4785–4790.
42. Austin PC, Lee DS, Fine JP, et al. Introduction to the analysis of survival data in the presence of competing risks. *Circulation.* 2016;133(6):601–609.
43. Lau B, Cole SR, Gange SJ. Competing risk regression models for epidemiologic data. *Am J Epidemiol.* 2009;170(2):244–256.
44. Sterne JAC, White IR, Carlin JB, et al. Multiple imputation for missing data in epidemiological and clinical research: Potential and pitfalls. *BMJ.* 2009; 338(b2393):1–19.
45. Land SR, Toll BA, Moinpour CM, et al. Research priorities, measures, and recommendations for assessment of tobacco use in clinical cancer research. *Clin Cancer Res.* 2016;(Cmd):1–24.