VOLUME 34 · NUMBER 12 · APRIL 20, 2016

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Cigarette Smoking Before and After Breast Cancer Diagnosis: Mortality From Breast Cancer and Smoking-Related Diseases

Michael N. Passarelli, Polly A. Newcomb, John M. Hampton, Amy Trentham-Dietz, Linda J. Titus, Kathleen M. Egan, John A. Baron, and Walter C. Willett

See accompanying editorial on page 1295

Michael N. Passarelli, University of California, San Francisco, San Francisco, CA; Polly A. Newcomb, Fred Hutchinson Cancer Research Center, Seattle, WA; Polly A. Newcomb, John M. Hampton, and Amy Trentham-Dietz, University of Wisconsin School of Medicine and Public Health, Madison, WI; Linda J. Titus, Geisel School of Medicine at Dartmouth, Lebanon, NH; Kathleen M. Egan, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL; John A. Baron, University of North Carolina School of Medicine, Chapel Hill, NC; and Walter C. Willett, Harvard Medical School and Brigham and Women's Hospital, Boston, MA.

Published online ahead of print at www.jco.org on January 25, 2016.

Funded by Grants No. R01CA47147, R01CA67264, R01CA47305, R01CA69664, R01CA82004, T32CA009168, R25CA112355, K05CA152714, P30CA014520, and P30CA015704 from the National Cancer Institute and by Susan G. Komen for the Cure Grant No. POP0504234.

M.N.P. and P.A.N. contributed equally to this work.

Presented at the 38th Annual Meeting of the American Society of Preventive Oncology, Arlington, VA, March 8-11, 2014.

Authors' disclosures of potential conflicts of interest are found in the article online at www.jco.org. Author contributions are found at the end of this article.

Corresponding Author: Michael N. Passarelli, PhD, Department of Epidemiology and Biostatistics, University of California, San Francisco, 1450 3rd St, Box 3110, San Francisco, CA 94143; e-mail: michael.passarelli@ucsf.edu.

0732-183X/16/3412w-1315w/$20.00

DOI: 10.1200/JCO.2015.63.9328

ABSTRACT

Purpose
Cigarette smoking increases overall mortality, but it is not established whether smoking is associated with breast cancer prognosis.

Methods
We evaluated the association between smoking status before and after breast cancer diagnosis and mortality in the Collaborative Breast Cancer and Women's Longevity Study, a population-based prospective observational study conducted in Wisconsin, New Hampshire, and Massachusetts. Participants included 20,691 women, ages 20 to 79 years, diagnosed with incident localized or regional invasive breast cancer between 1988 and 2008; a subset of 4,562 of these women were recontacted a median of 6 years after diagnosis. Hazard ratios (HRs) with 95% CIs were calculated according to smoking status for death as a result of breast cancer; cancers of the lung, pharynx, or intrathoracic organs; other cancer; respiratory disease; and cardiovascular disease.

Results
During a median of 12 years, 6,778 women died, including 2,894 who died as a result of breast cancer. Active smokers 1 year before breast cancer diagnosis were more likely than never smokers to die of breast cancer (HR, 1.25; 95% CI, 1.13 to 1.37), respiratory cancer (HR, 14.48; 95% CI, 9.89 to 21.21), other respiratory disease (HR, 6.02; 95% CI, 4.55 to 7.97), and cardiovascular disease (HR, 2.08; 95% CI, 1.80 to 2.41). The 10% of women who continued to smoke after diagnosis were more likely than never smokers to die of breast cancer (HR, 1.72; 95% CI, 1.13 to 2.60). When compared with women who continued to smoke after diagnosis, those who quit smoking after diagnosis had lower mortality from breast cancer (HR, 0.67; 95% CI, 0.38 to 1.19) and respiratory cancer (HR, 0.39; 95% CI, 0.16 to 0.95).

Conclusion
Smoking before or after diagnosis was associated with a higher mortality from breast cancer and several other causes.

J Clin Oncol 34:1315-1322. © 2016 by American Society of Clinical Oncology

INTRODUCTION

Cigarette smoking is responsible for nearly half of a million premature deaths in the United States annually,[1] and it continues to be one of the most important public health issues today.[2,3] Smoking affects hormone concentrations,[4] and a number of studies have observed that the association between smoking and the risk of developing breast cancer may depend on the years of smoking, the lifetime amount of smoking, and the age at initiation.[5-10] The 2014 Report of the Surgeon General on the health consequences of smoking concluded that there is sufficient evidence of biologic mechanisms by which breast cancer may be caused by smoking and suggestive, but not sufficient, evidence to infer a causal relationship.[11]

There are more than 3 million breast cancer survivors in the United States,[12] but only recently has adequate follow-up accrued in large cohorts to assess whether lifetime smoking is associated with long-term prognosis. Several studies have linked prediagnosis smoking history to higher risk of death as a result of breast cancer,[13-23] but very little is known about women who continue to smoke after diagnosis. To investigate cigarette smoking habits of breast cancer cases and mortality from breast cancer and other common

smoking-related causes of death, we analyzed data from the population-based Collaborative Breast Cancer Study (CBCS) and Collaborative Women's Longevity Study (CWLS).[24,25] The CBCS enrolled more than 22,000 women diagnosed with incident invasive breast cancer through a series of case-control studies, and the CWLS recontacted nearly 5,000 breast cancer survivors from the CBCS to assess postdiagnosis exposures and health events.

METHODS

CBCS

The CBCS consisted of multisite population-based case-control studies in New Hampshire, Massachusetts, and Wisconsin, which were conducted over a 20-year period beginning in 1988. The study enrolled women with incident invasive breast cancer diagnosed from age 20 to 74 years from 1988 to 1991, to age 79 years from 1992 to 1996, and to age 69 years from 1997 to 2008. In total, 23,344 women with breast cancer participated. All women completed a telephone interview, including a questionnaire to assess prediagnosis exposures and health histories. For recent exposures, participants were instructed to focus on those that occurred approximately 1 year before breast cancer diagnosis. The median time between diagnosis and completion of the CBCS questionnaire was approximately 16 months (interquartile range, 12 to 19 months). Additional details, including full eligibility criteria, data collection procedures, and participation rates, have been previously reported.[24,25] The CBCS protocols were approved by the institutional review boards of the medical centers at Dartmouth College, Harvard University, and the University of Wisconsin.

CWLS

Between 1998 and 2001, a total of 14,621 women with breast cancer from the CBCS known to still be alive were identified and invited to participate in the CWLS. Approximately 40% participated by completing a mailed questionnaire that focused on postdiagnosis exposures and health events. The median time between diagnosis and completion of the CWLS questionnaire was approximately 6 years (interquartile range, 3 to 9 years). Additional information on the design of the CWLS and the characteristics of participants also has been previously reported.[26-29] The CWLS protocols were approved at the same institutional review boards as the CBCS.

Ascertainment and Definition of Cigarette Smoking History

Women enrolled in the CBCS were asked to report whether they had smoked at least 100 cigarettes in their lifetime; their age at smoking initiation; the total years of smoking; the average number of cigarettes smoked per day; whether they continued to smoke 1 year before diagnosis (ie, recent smokers); and, for those who quit (ie, former smokers), their age at cessation. Pack-years were calculated for prediagnosis smokers by multiplying the average number of cigarettes smoked per day by the number of years smoked and dividing by 20 cigarettes per pack. Women in the CWLS were asked to report whether they were currently smoking cigarettes at the time of the questionnaire (ie, current smokers).

Ascertainment and Definition of Other Exposure Data

The CBCS interview collected information on demographics, height and weight, reproductive history (including parity, age at first birth, and menopausal status), use of medications (including exogenous hormones), alcohol consumption, mammography history, and first-degree family history of breast cancer. Menopause was defined as natural menopause, hysterectomy with bilateral oophorectomy, reaching age 55 years without bilateral oophorectomy, or hormone therapy use without bilateral oophorectomy. An alcoholic drink was defined as 12 ounces of beer, 5 ounces of red or white wine, or 1.5 ounces of spirits.[30] In addition to smoking history, the CWLS participants reported their height, weight, and alcohol consumption habits after diagnosis, as of the time of questionnaire completion.

Ascertainment and Definition of Tumor Characteristics and Mortality Data

Date of breast cancer diagnosis, stage of disease at diagnosis, and tumor histology were ascertained from state cancer registries according to summarization guidelines from the Surveillance, Epidemiology, and End Results program.[31] Vital status and cause of death were determined for all women in the CBCS, including those who later enrolled in the CWLS, by linkage to the National Death Index from the National Center for Health Statistics.[32] Identification of deaths was complete through December 31, 2009.

Underlying causes of death were classified into five broad groups according to the International Classification of Diseases (ICD), ninth revision[33] (before 1999) or tenth revision[34] (1999 and after): breast cancer; respiratory cancer, including neoplasms of the nasopharynx, larynx, trachea, bronchus, lung, pleura, and intrathoracic organs; other cancer; noncancer respiratory disease, including acute upper and lower respiratory infections and syndromes, influenza, pneumonia, bronchitis, emphysema, asthma, chronic obstructive pulmonary disease, and other respiratory disorders; and cardiovascular disease, including rheumatic heart disease, hypertensive heart disease, ischemic heart disease, pulmonary heart disease, cerebrovascular disease, arterial and/or vascular diseases, embolism, thrombosis, and other disorders of the circulatory system. ICD-9 and ICD-10 codes for these five groups are summarized in Appendix Table A1 (online only).

Statistical Analyses

Of the 23,344 CBCS participants, we excluded 188 women who were missing data on prediagnostic smoking status, 215 women for whom prediagnostic pack-years could not be calculated, 475 women diagnosed with distant-stage disease at diagnosis, 1,753 who had an unknown stage at diagnosis, and 22 women who were missing vital status. In total, 20,691 women with localized or regional-stage breast cancer were included in analyses of smoking before diagnosis.

For prediagnosis smoking considerations, survival time was calculated from the date of breast cancer diagnosis to the date of death or the end of follow-up. Cox proportional hazards regression with staggered entry was used to estimate adjusted hazard ratios (HR) and 95% CIs. Models stratified the baseline hazard on age at diagnosis, study phase, state of residence, and stage, and they adjusted for several potential confounding variables selected a priori, including education, body mass index, parous status, age at first birth, menopausal status, use of postmenopausal hormone therapy, mammography history, alcohol consumption, and first-degree family history of breast cancer. All adjustment variables were measured from the CBCS questionnaire and were intended to reflect exposures approximately 1 year before breast cancer diagnosis. A separate model was used for each cause of death.

Of 5,784 CWLS participants, a total of 5,168 were available for analyses after the exclusions we imposed on women in the CBCS. Additionally, we excluded 552 women who reported a breast cancer recurrence that occurred between the CBCS and CWLS questionnaires, and we excluded 45 women who indicated that they were in poor health at the time of the CWLS questionnaire. Nine women reported smoking after diagnosis who did not indicate smoking before diagnosis. Although smoking initiation after diagnosis was possible, misclassification is also a likely explanation, so we excluded these nine women. In total, 4,562 women with localized or regional-stage breast cancer at baseline were included in analyses of smoking after diagnosis.

For postdiagnosis smoking considerations, survival time was calculated from the date of return of the CWLS questionnaire to the date of death or the end of follow-up. Smoking status was parameterized to account for each possible pair of before/after diagnosis types (never/never, former/former, recent/former, recent/current). Proportional hazards

regression models for postdiagnosis smoking included the same covariates as models for prediagnostic smoking and included postdiagnosis body mass index, postdiagnosis alcohol consumption, and the number of years between date of diagnosis and return of the CWLS questionnaire. The assumption of proportion hazards was examined by testing for the statistical significance of interactions with log-transformed survival time. Statistical analyses were performed with SAS 9.3 (SAS Institute, Cary, NC). *P* values were two sided, and $P \leq .05$ was considered statistically significant.

RESULTS

Prediagnosis Cigarette Smoking and Mortality

Nearly all participants were white, and the mean age at diagnosis was 58 years (standard deviation, 11 years). Half of the women had ever smoked, and 20% reported actively smoking 1 year before breast cancer diagnosis. These recent smokers were generally younger, less educated, leaner, more likely to be heavy drinkers (≥ 10 drinks per week), and less likely to have undergone mammography screening than former or never smokers (Table 1). Compared with never smokers, those who quit before being diagnosed with breast cancer were more likely to have been postmenopausal, used hormone therapy, consumed alcohol, and undergone mammography. Never, former, and recent smokers had nearly identical distributions of localized and regional-stage disease at diagnosis.

A total of 6,778 deaths occurred over a median follow-up of 12 years. The two leading causes of death were breast cancer (2,894 deaths) and cardiovascular disease (1,394 deaths). Of 1,123 deaths as a result of cancers other than breast, 294 deaths were results of malignancies of the pharynx, lung, or intrathoracic organs. Prediagnostic recent smokers, but not former smokers, were more likely than never smokers to die of breast cancer (Table 2). The highest relative risks of death as a result of breast cancer were observed among long-term smokers (≥ 30 years), high–pack-year smokers (≥ 30 pack years), and former smokers having quit fewer than 5 years before breast cancer diagnosis (Table 3). Both former and recent smokers had higher mortality from noncancer respiratory diseases (367 deaths total) and cardiovascular diseases (Appendix Table A2). HR estimates were substantially higher for those who reported increasing duration of smoking and number of lifetime pack years, particularly for recent smokers, as well as for those who reported fewer years since quitting.

Postdiagnosis Cigarette Smoking and Mortality

The CWLS subcohort was generally similar to the entire CBCS cohort with regard to baseline characteristics, including age (mean, 59 years for CWLS *v* 58 years for CBCS) and stage at breast cancer diagnosis (73% localized for CWLS *v* 68% localized for CBCS; Appendix Table A3). A total of 434 women (10%) reported actively smoking after their breast cancer diagnoses (Appendix Table A4). During a median follow-up of 11 years from return of the postdiagnosis questionnaire, 988 deaths occurred. The two leading causes of death were cardiovascular disease (258 deaths) and breast cancer (246 deaths).

In the CWLS subcohort, ever smoking before or after diagnosis was associated with higher overall mortality and with risk of death from breast cancer (Table 4) and from respiratory cancer, noncancer respiratory disease, and cardiovascular disease (Appendix Table A5). Associations were strongest for women still smoking after breast cancer diagnosis and who had heavy usage (Table 5). Women who quit after diagnosis had elevated breast cancer mortality relative to never smokers, but the difference was not statistically significant (HR, 1.15; 95% CI, 0.70 to 1.90). Conversely, women who quit a minimum of 1 year before diagnosis had equivalent breast cancer mortality as never smokers (HR, 0.98; 95% CI, 0.72 to 1.34). Although not reaching statistical significance, when compared with women who continued to smoke after diagnosis (a change in reference group from Table 4), those who quit smoking after diagnosis had lower mortality from breast cancer (HR, 0.67; 95% CI, 0.38 to 1.19) and all causes (HR, 0.91; 95% CI, 0.67 to 1.20).

DISCUSSION

In this large prospective study of breast cancer survivors, recent prediagnostic cigarette smokers were 25% more likely to die of breast cancer than were those who never smoked. Although not statistically significant, the women who quit smoking after their breast cancer diagnosis had 33% lower risk of death as a result of breast cancer than did women who continued to smoke after diagnosis. Postdiagnosis quitters had a 9% lower risk of death as a result of all causes than postdiagnosis smokers; this difference included a statistically significant 60% lower risk of death from respiratory cancer and a 20% lower risk of death as a result of cardiovascular disease. Whether these findings are suggestive of a biologic mechanism related to the carcinogenic properties of tobacco smoke on tumor progression and metastasis or are related to demographic, behavioral, or clinical factors is presently unclear.

This is, to our knowledge, the largest study to date of survival outcomes according to smoking habits in women with a history of breast cancer. The After Breast Cancer Pooling Project,[35] a collaboration of three American cohort studies that enrolled nearly 10,000 patients with breast cancer, of whom approximately 1,000 had died of the disease, reported a statistically significant higher mortality from breast cancer for active smokers near the time of diagnosis relative to never smokers (HR, 1.61; 95% CI, 1.28 to 2.03).[22] A separate data pooling effort from five American cohort studies that collectively observed 2,022 deaths from breast cancer reported a more modest association (HR, 1.3; 95% CI, 1.2 to 1.5).[23]

The CWLS is unique in the assessment of smoking habits both before and after diagnosis. The Life After Cancer Epidemiology study enrolled women with breast cancer, on average, approximately 2 years after diagnosis (observing 244 deaths as a result of breast cancer among 2,258 with the disease) and reported a strong association with breast cancer–specific mortality for smokers relative to never smokers at their baseline assessment (HR, 2.01; 95% CI, 1.27 to 3.18).[19] In contrast, we used separate baseline and postdiagnosis assessments, which permitted us to distinguish prediagnosis and postdiagnosis quitters among former smokers. In addition to characterizing smoking habits, including amount and duration, the postdiagnosis assessment allowed incorporation of important covariates that may have changed after diagnosis, such as alcohol consumption[36] and body mass index.[37] The relatively long follow-up period for the CWLS allowed us to

Table 1. Characteristics at Breast Cancer Diagnosis According to Cigarette Smoking Status Before Diagnosis

Characteristic at Diagnosis	No. (%) of Patients			
		By Cigarette Smoking Status Before Diagnosis*		
	Total (N = 20,691)	Never (n = 10,399)	Former (n = 6,233)	Recent (n = 4,059)
Age, years				
< 50	4,872 (24)	2,492 (24)	1,206 (19)	1,174 (29)
50-59	6,106 (30)	2,842 (27)	1,947 (31)	1,317 (32)
60-69	7,047 (34)	3,475 (33)	2,324 (37)	1,248 (31)
70-79	2,666 (13)	1,590 (15)	756 (12)	320 (8)
State of residence				
New Hampshire	1,262 (6)	532 (5)	457 (7)	273 (7)
Massachusetts	4,870 (24)	2,123 (20)	1,653 (27)	1,094 (27)
Wisconsin	14,559 (70)	7,744 (74)	4,123 (66)	2,692 (66)
Education				
Less than high school	2,299 (11)	1,193 (12)	576 (9)	530 (13)
High school or some college	13,714 (67)	6,596 (64)	4,168 (67)	2,950 (73)
College degree	3,065 (15)	1,686 (16)	966 (16)	413 (10)
Professional or graduate degree	1,546 (8)	885 (9)	509 (8)	152 (4)
Unknown	67 (—)	39 (—)	14 (—)	14 (—)
Body mass index, kg/m^2*				
< 18.5	347 (2)	134 (1)	74 (1)	139 (3)
18.5-24.9	9,720 (48)	4,605 (45)	2,858 (46)	2,257 (56)
25.0-29.9	6,342 (31)	3,288 (32)	1,949 (32)	1,105 (27)
≥ 30	4,047 (20)	2,238 (22)	1,286 (21)	523 (13)
Unknown	235 (—)	134 (—)	66 (—)	35 (—)
Parous				
No	2,790 (14)	1,451 (14)	779 (13)	560 (14)
Yes	17,826 (86)	8,910 (86)	5,436 (87)	3,480 (86)
Unknown	75 (—)	38 (—)	18 (—)	19 (—)
Age at first birth, years†				
< 20	2,791 (16)	1,167 (13)	863 (16)	761 (22)
20-24	8,194 (46)	4,012 (45)	2,536 (47)	1,646 (47)
25-29	4,682 (26)	2,557 (29)	1,365 (25)	760 (22)
≥ 30	2,123 (12)	1,156 (13)	662 (12)	305 (9)
Unknown	36 (—)	18 (—)	10 (—)	8 (—)
Postmenopausal*				
No	5,365 (27)	2,808 (29)	1,408 (24)	1,149 (30)
Yes	14,206 (73)	7,042 (71)	4,486 (76)	2,678 (70)
Unknown	1,120 (—)	549 (—)	339 (—)	232 (—)
Postmenopausal hormone use*‡				
Never	7,572 (60)	3,807 (61)	2,271 (56)	1,494 (64)
Former	1,467 (12)	715 (11)	501 (12)	251 (11)
Recent	3,561 (28)	1,701 (27)	1,286 (32)	574 (25)
Unknown	1,606 (—)	819 (—)	428 (—)	359 (—)
Recent alcohol consumer*				
No	3,879 (19)	2,305 (22)	951 (15)	623 (16)
Yes	16,700 (81)	8,040 (78)	5,265 (85)	3,395 (84)
Unknown	112 (—)	54 (—)	17 (—)	41 (—)
Alcoholic drinks per week*§				
≤ 2	10,422 (62)	5,768 (72)	2,903 (55)	1,751 (52)
3-6	3,226 (19)	1,378 (17)	1,166 (22)	682 (20)
7-9	1,480 (9)	513 (6)	600 (11)	367 (11)
≥ 10	1,572 (9)	381 (5)	596 (11)	595 (18)
Mammography in lifetime*				
No	3,923 (22)	1,983 (22)	974 (18)	966 (29)
Yes	13,883 (78)	7,075 (78)	4,472 (82)	2,336 (71)
Unknown	2,885 (—)	1,341 (—)	787 (—)	757 (—)
First-degree family history of breast cancer				
No	16,099 (79)	8,156 (80)	4,814 (79)	3,129 (79)
Yes	4,196 (21)	2,066 (20)	1,307 (21)	823 (21)
Unknown	396 (—)	177 (—)	112 (—)	107 (—)
Stage				
Localized	14,043 (68)	6,957 (67)	4,321 (69)	2,765 (68)
Regional	6,648 (32)	3,442 (33)	1,912 (31)	1,294 (32)

*As of 1 year before diagnosis.
†Among parous women.
‡Among postmenopausal women.
§Among recent alcohol consumers.

Table 2. Association Between Cigarette Smoking Status Before Diagnosis and Death As a Result of Breast Cancer and All Causes

Cigarette Smoking Status Before Diagnosis	No. (%) of Patients (N = 20,691)	Cause of Death: Breast Cancer — No. of Deaths (n = 2,894)	Breast Cancer — HR* (95% CI)	All Causes — No. of Deaths (n = 6,778)	All Causes — HR* (95% CI)
Never smoker	10,399 (50)	1,448	1 (Reference)	3,234	1 (Reference)
Former smoker	6,233 (30)	755	0.93 (0.85 to 1.02)	1,910	1.11 (1.05 to 1.17)
Recent smoker	4,059 (20)	691	1.25 (1.13 to 1.37)	1,634	1.67 (1.57 to 1.79)

Abbreviation: HR, hazard ratio.
*HR stratified by age at diagnosis, study phase, state of residence, and stage at diagnosis and adjusted for education, body mass index, parous status, age at first birth, menopausal status, use of postmenopausal hormone therapy, mammography history, alcohol consumption, and first-degree family history of breast cancer.

comprehensively evaluate several different causes of death, including respiratory diseases that have not traditionally been assessed as outcomes in studies of breast cancer. Confidence in our results for breast cancer–specific mortality are bolstered by the striking, but expected, magnitude of associations observed for respiratory cancer, respiratory disease, and cardiovascular disease.

We acknowledge a few specific study limitations. It is possible that cancer survivors may misrepresent their smoking status.[38] However, the observed prevalence of current smoking among long-term breast cancer survivors (10%) was consistent with previous reports.[39,40] Participants were provided only a single occasion to report postdiagnosis smoking habits, and we do not know whether women who reported actively smoking at the time of the CWLS questionnaire quit smoking thereafter. Although we evaluated duration and intensity of smoking, we did not observe evidence of a trend in breast cancer or overall mortality for age at smoking initiation and for smoking status before first full-term pregnancy (data not shown). Lifetime exposure to second-hand smoke was not considered.

Table 3. Association Between Duration of Cigarette Smoking, Amount of Cigarette Smoking, and Years Since Quit Before Diagnosis and Death As a Result of Breast Cancer and All Causes

Cigarette Smoking Variable Before Diagnosis	No. (%) of Patients (N = 20,691)	Cause of Death: Breast Cancer — No. of Deaths (n = 2,894)	Breast Cancer — HR* (95% CI)	All Causes — No. of Deaths (n = 6,778)	All Causes — HR* (95% CI)
Duration of smoking, years					
Never smoker	10,399 (50)	1,448	1 (Reference)	3,234	1 (Reference)
Former smoker					
< 15	2,376 (11)	275	0.92 (0.81 to 1.05)	480	0.95 (0.86 to 1.04)
15 to < 30	2,132 (10)	238	0.82 (0.71 to 0.94)	562	0.95 (0.87 to 1.04)
≥ 30	1,725 (8)	242	1.10 (0.95 to 1.27)	868	1.39 (1.29 to 1.50)
Recent smoker					
< 15	187 (1)	41	1.36 (0.99 to 1.88)	54	1.36 (1.03 to 1.79)
15 to < 30	1,104 (5)	188	1.07 (0.91 to 1.26)	273	1.21 (1.06 to 1.39)
≥ 30	2,768 (13)	462	1.32 (1.18 to 1.47)	1,307	1.81 (1.69 to 1.94)
Amount of smoking, pack-years					
Never smoker	10,399 (50)	1,448	1 (Reference)	3,234	1 (Reference)
Former smoker					
< 15	3,448 (17)	406	0.91 (0.82 to 1.02)	858	0.98 (0.90 to 1.05)
15 to < 30	1,314 (6)	153	0.87 (0.73 to 1.03)	400	1.07 (0.96 to 1.19)
≥ 30	1,471 (7)	196	1.05 (0.90 to 1.23)	652	1.41 (1.29 to 1.54)
Recent smoker					
< 15	768 (4)	130	1.12 (0.93 to 1.35)	218	1.21 (1.05 to 1.40)
15 to < 30	1,126 (5)	180	1.10 (0.94 to 1.29)	379	1.49 (1.33 to 1.66)
≥ 30	2,165 (11)	381	1.39 (1.23 to 1.56)	1,037	1.92 (1.78 to 2.06)
Years since quit					
Never smoker	10,399 (50)	1,448	1 (Reference)	3,234	1 (Reference)
≥ 25	1,660 (8)	175	0.93 (0.79 to 1.09)	459	0.97 (0.87 to 1.07)
15 to < 25	1,713 (8)	189	0.84 (0.72 to 0.98)	457	1.00 (0.90 to 1.10)
10 to < 15	939 (5)	104	0.82 (0.67 to 1.00)	272	1.05 (0.92 to 1.19)
5 to < 10	1,122 (5)	152	0.97 (0.82 to 1.15)	392	1.26 (1.13 to 1.40)
< 5	799 (4)	135	1.20 (1.00 to 1.44)	330	1.52 (1.35 to 1.71)
Recent smoker	4,059 (20)	691	1.25 (1.13 to 1.38)	1,634	1.68 (1.58 to 1.80)

Abbreviation: HR, hazard ratio.
*HR stratified by age at diagnosis, study phase, state of residence, and stage at diagnosis and adjusted for education, body mass index, parous status, age at first birth, menopausal status, use of postmenopausal hormone therapy, mammography history, alcohol consumption, and first-degree family history of breast cancer.

Table 4. Association Between Cigarette Smoking Status Before and After Diagnosis and Death As a Result of Breast Cancer and All Causes

Cigarette Smoking Status Before and After Diagnosis	No. (%) of Patients (N = 4,562)	Cause of Death: Breast Cancer, No. of Deaths (n = 246)	Cause of Death: Breast Cancer, HR* (95% CI)	Cause of Death: All Causes, No. of Deaths (n = 988)	Cause of Death: All Causes, HR* (95% CI)
Never/never	2,219 (49)	116	1 (Reference)	421	1 (Reference)
Former/former	1,557 (34)	75	0.98 (0.72 to 1.34)	342	1.45 (1.24 to 1.69)
Recent/former	352 (8)	20	1.15 (0.70 to 1.90)	103	2.34 (1.85 to 2.96)
Recent/current	434 (10)	35	1.72 (1.13 to 2.60)	122	2.57 (2.06 to 3.21)

Abbreviation: HR, hazard ratio.
*HR stratified by age at diagnosis, study phase, state of residence, and stage at diagnosis and adjusted for education, body mass index, parous status, age at first birth, menopausal status, use of postmenopausal hormone therapy, mammography history, alcohol consumption, first-degree family history of breast cancer, postdiagnosis body mass index, postdiagnosis alcohol consumption, and time from diagnosis to postdiagnosis questionnaire.

On the basis of the CBCS and CWLS designs, the postdiagnosis subcohort included women with varied lengths of time since diagnosis. Postdiagnosis HRs were calculated with respect to time from follow-up questionnaire, not diagnosis. We adjusted for the duration between diagnosis and questionnaire return, but we found that results were not substantially different without this adjustment. In light of these considerations, our results are probably most generalizable to the population of long-term breast cancer survivors.

We attempted to control for confounding by using multivariable regression and baseline hazard stratification. Statistical models accounted for several breast cancer risk factors that we hypothesized may also be related to survival and to stage at diagnosis and mammography screening history. Alcohol consumption and body mass index, important disease risk factors also potentially related to survival and highly associated with cigarette smoking habits, were included in models for prediagnosis smoking and in models for postdiagnosis smoking by using updated measurements from the CWLS questionnaire.

We lacked information on hormone receptor status of breast tumors and could not separately evaluate breast cancer mortality by estrogen-receptor, progesterone-receptor, or human epidermal

Table 5. Association Between Duration of Cigarette Smoking, Amount of Cigarette Smoking, and Years Since Quit Before and After Diagnosis and Death As a Result of Breast Cancer and All Causes

Cigarette Smoking Variable Before and After Diagnosis	No. (%) of Patients (N = 4,562)	Cause of Death: Breast Cancer, No. of Deaths (n = 246)	Cause of Death: Breast Cancer, HR* (95% CI)	Cause of Death: All Causes, No. of Deaths (n = 988)	Cause of Death: All Causes, HR* (95% CI)
Duration of smoking, years†					
Never/never	2,219 (49)	116	1 (Reference)	421	1 (Reference)
Former/former					
< 30	1,135 (25)	54	0.92 (0.65 to 1.30)	192	1.27 (1.06 to 1.52)
≥ 30	422 (9)	21	1.18 (0.72 to 1.93)	150	1.77 (1.45 to 2.16)
Recent/former					
< 30	94 (2)	9	1.59 (0.77 to 3.27)	19	2.32 (1.42 to 3.79)
≥ 30	258 (6)	11	0.93 (0.49 to 1.78)	84	2.33 (1.81 to 2.99)
Recent/current					
< 30	111 (2)	11	1.94 (0.98 to 3.85)	17	1.92 (1.14 to 3.23)
≥ 30	323 (7)	24	1.63 (1.01 to 2.64)	105	2.69 (2.13 to 3.41)
Amount of smoking, pack-years†					
Never/never	2,219 (49)	116	1 (Reference)	421	1 (Reference)
Former/former					
< 30	1,205 (26)	54	0.89 (0.63 to 1.25)	232	1.30 (1.10 to 1.54)
≥ 30	352 (8)	21	1.38 (0.84 to 2.26)	110	1.96 (1.56 to 2.45)
Recent/former					
< 30	168 (4)	10	1.00 (0.51 to 1.97)	39	1.84 (1.30 to 2.61)
≥ 30	184 (4)	10	1.36 (0.69 to 2.67)	64	2.81 (2.12 to 3.73)
Recent/current					
< 30	183 (4)	12	1.39 (0.74 to 2.62)	36	1.86 (1.30 to 2.66)
≥ 30	251 (6)	23	1.94 (1.19 to 3.17)	86	3.09 (2.39 to 4.00)

Abbreviation: HR, hazard ratio.
*HR stratified by age at diagnosis, study phase, state of residence, and stage at diagnosis and adjusted for education, body mass index, parous status, age at first birth, menopausal status, use of postmenopausal hormone therapy, mammography history, alcohol consumption, first-degree family history of breast cancer, postdiagnosis body mass index, postdiagnosis alcohol consumption, and time from diagnosis to postdiagnosis questionnaire.
†Duration and pack-years calculated for smoking before diagnosis.

growth factor receptor 2 (HER2)/neu-status. Evidence of whether the risk of developing hormone receptor–positive breast cancer depends on smoking history is inconsistent.[41-43] Detailed information on second primaries and treatment of breast cancer was also unavailable; thus, we could not evaluate the possibility that smokers differentially have diminished efficacy of some treatments or suffer from late effects of therapy, including cardiotoxicity.[44,45] Our study was observational, and variables unaccounted for in our analyses may contribute to confound the association between cigarette smoking and breast cancer death. A randomized controlled study of women diagnosed with breast cancer that compares aggressive smoking cessation strategies to standard practice would help establish a causal link.

Attributions of cause of death in those with cancer may depend on numerous factors related to the long-term care of the patient.[46] In the CBCS cohort, fewer women died of breast cancer (n = 2,894) than as a result of all other causes (n = 3,884). We did not use competing risks models, which may explain why some estimated HRs for breast cancer survival are less than 1 in comparisons of former to never smokers. Any cause-specific reduced risk of death as a result of smoking likely reflects the overwhelming higher risk of death as a result of another cause. Nonetheless, these results underline the severity of comorbidities faced by both active and former smokers with a history of breast cancer.

This large population-based study clarifies the long-term adverse health consequences of women who quit smoking before breast cancer diagnosis, those who quit smoking after breast cancer diagnosis, and those who continue to smoke after breast cancer diagnosis. Regardless of a diagnosis of breast cancer, smokers should undergo recommended respiratory and cardiovascular disease surveillance to reduce smoking-related mortality. Our study reinforces the importance of cigarette smoking cessation in women with breast cancer.[47-49] For the minority of breast cancer survivors who continue to smoke after their diagnoses, these results should provide additional motivation to quit.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

AUTHOR CONTRIBUTIONS

Conception and design: Polly A. Newcomb, Walter C. Willett
Financial support: Polly A. Newcomb, Linda J. Titus
Provision of study materials or patients: Polly A. Newcomb, Linda J. Titus
Collection and assembly of data: Polly A. Newcomb, Linda J. Titus
Data analysis and interpretation: All authors
Manuscript writing: All authors
Final approval of manuscript: All authors

REFERENCES

1. Centers for Disease Control and Prevention: Smoking-attributable mortality, years of potential life lost, and productivity losses: United States, 2000-2004. Morb Mortal Wkly Rep 57:1226-1228, 2008
2. Thun MJ, Carter BD, Feskanich D, et al: 50-year trends in smoking-related mortality in the United States. N Engl J Med 368:351-364, 2013
3. Jha P, Ramasundarahettige C, Landsman V, et al: 21st-century hazards of smoking and benefits of cessation in the United States. N Engl J Med 368: 341-350, 2013
4. Endogenous Hormones and Breast Cancer Collaborative Group: Circulating sex hormones and breast cancer risk factors in postmenopausal women: Reanalysis of 13 studies. Br J Cancer. 2011; 105:709-722, 2011
5. Terry PD, Rohan TE: Cigarette smoking and the risk of breast cancer in women: A review of the literature. Cancer Epidemiol Biomarkers Prev 11: 953-971, 2002
6. International Agency for Research on Cancer Monograph on the Evaluation of Carcinogenic Risks to Humans: Tobacco Smoke and Involuntary Smoking. International Agency for Research on Cancer, Lyon, France, 2004.
7. Gram IT, Braaten T, Terry PD, et al: Breast cancer risk among women who start smoking as teenagers. Cancer Epidemiol Biomarkers Prev 14: 61-66, 2005
8. Luo J, Margolis KL, Wactawski-Wende J, et al: Association of active and passive smoking with risk of breast cancer among postmenopausal women: A prospective cohort study. BMJ 342:d1016, 2011
9. Gaudet MM, Gapstur SM, Sun J, et al: Active smoking and breast cancer risk: Original cohort data and meta-analysis. J Natl Cancer Inst 105:515-525, 2013
10. Land SR, Liu Q, Wickerham DL, et al: Cigarette smoking, physical activity, and alcohol consumption as predictors of cancer incidence among women at high risk of breast cancer in the NSABP P-1 trial. Cancer Epidemiol Biomarkers Prev 23:823-832, 2014
11. Centers for Disease Control and Prevention: The Health Consequences of Smoking: 50 Years of Progress—A Report of the Surgeon General. United States Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, Atlanta, GA, 2014.
12. DeSantis CE, Lin CC, Mariotto AB, et al: Cancer treatment and survivorship statistics, 2014. CA Cancer J Clin 64:252-271, 2014
13. Ewertz M, Gillanders S, Meyer L, et al: Survival of breast cancer patients in relation to factors which affect the risk of developing breast cancer. Int J Cancer 49:526-530, 1991
14. Manjer J, Andersson I, Berglund G, et al: Survival of women with breast cancer in relation to smoking. Eur J Surg 166:852-858, 2000
15. Fentiman IS, Allen DS, Hamed H: Smoking and prognosis in women with breast cancer. Int J Clin Pract 59:1051-1054, 2005
16. Sagiv SK, Gaudet MM, Eng SM, et al: Active and passive cigarette smoke and breast cancer survival. Ann Epidemiol 17:385-393, 2007
17. Holmes MD, Murin S, Chen WY, et al: Smoking and survival after breast cancer diagnosis. Int J Cancer 120:2672-2677, 2007
18. Barnett GC, Shah M, Redman K, et al: Risk factors for the incidence of breast cancer: Do they affect survival from the disease? J Clin Oncol 26: 3310-3316, 2008
19. 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 136:521-533, 2012
20. Warren GW, Kasza KA, Reid ME, et al: Smoking at diagnosis and survival in cancer patients. Int J Cancer 132:401-410, 2013
21. Bérubé S, Lemieux J, Moore L, et al: Smoking at time of diagnosis and breast cancer-specific survival: New findings and systematic review with meta-analysis. Breast Cancer Res 16:R42, 2014
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 106:djt359, 2014
23. Carter BD, Abnet CC, Feskanich D, et al: Smoking and mortality: Beyond established causes. N Engl J Med 372:631-640, 2015
24. Newcomb PA, Storer BE, Longnecker MP, et al: Lactation and a reduced risk of premenopausal breast cancer. N Engl J Med 330:81-87, 1994
25. Newcomb PA, Trentham-Dietz A, Hampton JM, et al: Late age at first full-term birth is strongly associated with lobular breast cancer. Cancer 117: 1946-1956, 2011
26. Holick CN, Newcomb PA, Trentham-Dietz A, et al: Physical activity and survival after diagnosis of invasive breast cancer. Cancer Epidemiol Biomarkers Prev 17:379-386, 2008
27. Nichols HB, Trentham-Dietz A, Egan KM, et al: Body mass index before and after breast cancer diagnosis: Associations with all-cause,

breast cancer, and cardiovascular disease mortality. Cancer Epidemiol Biomarkers Prev 18: 1403-1409, 2009

28. Beasley JM, Newcomb PA, Trentham-Dietz A, et al: Post-diagnosis dietary factors and survival after invasive breast cancer. Breast Cancer Res Treat 128: 229-236, 2011

29. Newcomb PA, Kampman E, Trentham-Dietz A, et al: Alcohol consumption before and after breast cancer diagnosis: Associations with survival from breast cancer, cardiovascular disease, and other causes. J Clin Oncol 31:1939-1946, 2013

30. National Institute on Alcohol Abuse and Alcoholism: Rethinking Drinking: Alcohol and Your Health. National Institutes of Health, Bethesda, MD, 2012.

31. Young JL Jr, Roffers SD, Ries LAG, et al (eds): SEER Summary Staging Manual 2000: Codes and Coding Instructions. National Cancer Institute, Bethesda, MD. 2001.

32. Calle EE, Terrell DD: Utility of the National Death Index for ascertainment of mortality among Cancer Prevention Study II participants. Am J Epidemiol 137:235-241, 1993

33. International Classification of Diseases, Ninth Revision. Geneva, Switzerland, World Health Organization, 1977

34. International Classification of Diseases, Tenth Revision. Geneva, Switzerland, World Health Organization, 1992

35. Nechuta SJ, Caan BJ, Chen WY, et al: The After Breast Cancer Pooling Project: Rationale, methodology, and breast cancer survivor characteristics. Cancer Causes Control 22:1319-1331, 2011

36. Hamajima N, Hirose K, Tajima K, et al; Collaborative Group on Hormonal Factors in Breast Cancer: 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 87:1234-1245, 2002

37. Morimoto LM, White E, Chen Z, et al: Obesity, body size, and risk of postmenopausal breast cancer: The Women's Health Initiative (United States). Cancer Causes Control 13:741-751, 2002

38. Morales NA, Romano MA, Michael Cummings K, et al: Accuracy of self-reported tobacco use in newly diagnosed cancer patients. Cancer Causes Control 24:1223-1230, 2013

39. Mayer DK, Carlson J: Smoking patterns in cancer survivors. Nicotine Tob Res 13:34-40, 2011

40. Westmaas JL, Alcaraz KI, Berg CJ, et al: Prevalence and correlates of smoking and cessation-related behavior among survivors of ten cancers: Findings from a nationwide survey nine years after diagnosis. Cancer Epidemiol Biomarkers Prev 23: 1783-1792, 2014

41. London SJ, Colditz GA, Stampfer MJ, et al: Prospective study of smoking and the risk of breast cancer. J Natl Cancer Inst 81:1625-1631, 1989

42. Morabia A, Bernstein M, Ruiz J, et al: Relation of smoking to breast cancer by estrogen receptor status. Int J Cancer 75:339-342, 1998

43. Kawai M, Malone KE, Tang MTC, et al: Active smoking and the risk of estrogen receptor–positive and triple-negative breast cancer among women ages 20 to 44 years. Cancer 120:1026-1034, 2014

44. Doyle JJ, Neugut AI, Jacobson JS, et al: Chemotherapy and cardiotoxicity in older breast cancer patients: A population-based study. J Clin Oncol 23:8597-8605, 2005

45. Hooning MJ, Botma A, Aleman BM, et al: Long-term risk of cardiovascular disease in 10-year survivors of breast cancer. J Natl Cancer Inst 99: 365-375, 2007

46. Black WC, Haggstrom DA, Welch HG: All-cause mortality in randomized trials of cancer screening. J Natl Cancer Inst 94:167-173, 2002

47. Toll BA, Brandon TH, Gritz ER, et al; AACR Subcommittee on Tobacco and Cancer: Assessing tobacco use by cancer patients and facilitating cessation: An American Association for Cancer Research policy statement. Clin Cancer Res 19:1941-1948, 2013

48. Sitas F, Weber MF, Egger S, et al: Smoking cessation after cancer. J Clin Oncol 32:3593-3595, 2014

49. Karam-Hage M, Cinciripini PM, Gritz ER: Tobacco use and cessation for cancer survivors: An overview for clinicians. CA Cancer J Clin 64:272-290, 2014

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Cigarette Smoking Before and After Breast Cancer Diagnosis: Mortality From Breast Cancer and Smoking-Related Diseases

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or jco.ascopubs.org/site/ifc.

Michael N. Passarelli
No relationship to disclose.

Polly A. Newcomb
No relationship to disclose.

John M. Hampton
No relationship to disclose.

Amy Trentham-Dietz
No relationship to disclose.

Linda J. Titus
No relationship to disclose.

Kathleen M. Egan
No relationship to disclose.

John A. Baron
Patents, Royalties, Other Intellectual Property: Together with Dartmouth College, I hold a use patent for chemopreventive use of calcium. This is currently not licensed. Together with Dartmouth College, I hold a use patent for the colorectal chemopreventive use of aspirin. This is currently not licensed.

Walter C. Willett
No relationship to disclose.

Appendix

Table A1. Summary of Underlying Cause of Death Classifications

Underlying cause of death	Classification Code	
	ICD-9	ICD-10
Breast cancer	174	C50
Respiratory cancer	160-165	C30-C39
Other cancer	140-159, 170-173, 175-209, 235-239	C00-C26, C40-C49, C51-C97, D37-D48
Noncancer respiratory disease	460-519	J00-J99
Cardiovascular disease	390-459	I00-I99

Abbreviations: ICD-9, International Classification of Diseases, ninth revision; ICD-10, International Classification of Diseases, tenth revision.

Table A2. Association Between Cigarette Smoking Status, Duration, and Quantity Before Diagnosis and Death As a Result of Cancer and Noncancer Causes

Cigarette smoking variable before diagnosis	No. (%) of Patients (N = 20,691)	Cause of Death: Respiratory Cancer* No. of Deaths (n = 294)	Respiratory Cancer* HR§ (95% CI)	Other Cancer No. of Deaths (n = 829)	Other Cancer HR§ (95% CI)	Noncancer Respiratory Disease† No. of Deaths (n = 367)	Noncancer Respiratory Disease† HR§ (95% CI)	Cardiovascular Disease‡ No. of Deaths (n=1,394)	Cardiovascular Disease‡ HR§ (95% CI)
Smoking status									
Never smoker	10,399 (50)	35	1 (Reference)	417	1 (Reference)	98	1 (Reference)	688	1 (Reference)
Former smoker	6,233 (30)	81	3.76 (2.51 to 5.63)	260	1.08 (0.92 to 1.27)	125	2.57 (1.96 to 3.38)	398	1.21 (1.07 to 1.38)
Recent smoker	4,059 (20)	178	14.48 (9.89 to 21.21)	152	1.14 (0.93 to 1.39)	144	6.02 (4.55 to 7.97)	308	2.08 (1.80 to 2.41)
Duration of smoking, years									
Never smoker	10,399 (50)	35	1 (Reference)	417	1 (Reference)	98	1 (Reference)	688	1 (Reference)
Former smoker									
< 15	2,376 (11)	9	1.57 (0.75 to 3.30)	63	0.95 (0.72 to 1.25)	11	1.00 (0.53 to 1.87)	60	0.86 (0.65 to 1.12)
15 to < 30	2,132 (10)	19	2.50 (1.42 to 4.41)	84	1.00 (0.79 to 1.27)	23	1.40 (0.87 to 2.24)	109	1.03 (0.84 to 1.27)
≥ 30	1,725 (8)	53	6.29 (4.06 to 9.74)	113	1.25 (1.01 to 1.54)	91	4.20 (3.12 to 5.64)	229	1.50 (1.29 to 1.76)
Recent smoker									
< 15	187 (1)	1	3.14 (0.42 to 23.57)	3	0.74 (0.23 to 2.33)	1	1.64 (0.22 to 12.19)	2	0.63 (0.16 to 2.55)
15 to < 30	1,104 (5)	16	7.65 (3.89 to 15.04)	21	0.99 (0.62 to 1.58)	9	3.16 (1.48 to 6.71)	26	1.88 (1.24 to 2.85)
≥ 30	2,768 (13)	161	15.48 (10.54 to 22.72)	128	1.18 (0.95 to 1.45)	134	6.35 (4.78 to 8.44)	280	2.13 (1.83 to 2.47)
Amount of smoking, pack-years									
Never smoker	10,399 (50)	35	1 (Reference)	417	1 (Reference)	98	1 (Reference)	688	1 (Reference)
Former smoker									
< 15	3,448 (17)	19	1.86 (1.06 to 3.27)	121	1.00 (0.81 to 1.23)	26	1.09 (0.70 to 1.70)	157	1.02 (0.85 to 1.22)
15 to < 30	1,314 (6)	14	2.97 (1.59 to 5.56)	52	0.99 (0.74 to 1.32)	29	2.79 (1.83 to 4.25)	95	1.33 (1.07 to 1.65)
≥ 30	1,471 (7)	48	7.76 (4.95 to 12.18)	87	1.30 (1.02 to 1.65)	70	4.89 (3.55 to 6.74)	146	1.44 (1.20 to 1.73)
Recent smoker									
< 15	768 (4)	12	6.56 (3.33 to 12.91)	16	0.73 (0.44 to 1.21)	8	2.17 (1.04 to 4.53)	29	1.29 (0.89 to 1.89)
15 to < 30	1,126 (5)	21	7.39 (4.22 to 12.93)	37	1.17 (0.83 to 1.66)	19	3.61 (2.17 to 6.02)	87	2.72 (2.15 to 3.43)
≥ 30	2,165 (11)	145	19.24 (13.03 to 28.40)	99	1.24 (0.98 to 1.56)	117	7.98 (5.94 to 10.72)	192	2.06 (1.73 to 2.45)
Years since quit									
Never smoker	10,399 (50)	35	1 (Reference)	417	1 (Reference)	98	1 (Reference)	688	1 (Reference)
≥ 25	1,660 (8)	8	1.33 (0.61 to 2.89)	70	1.00 (0.77 to 1.30)	20	1.30 (0.79 to 2.15)	99	0.96 (0.77 to 1.19)
15 to < 25	1,713 (8)	19	3.24 (1.83 to 5.74)	68	1.06 (0.82 to 1.38)	22	1.77 (1.11 to 2.82)	92	1.12 (0.90 to 1.40)
10 to < 15	939 (5)	16	5.61 (3.07 to 10.22)	39	1.13 (0.81 to 1.57)	20	2.68 (1.64 to 4.37)	63	1.27 (0.97 to 1.65)
5 to < 10	1,122 (5)	20	4.98 (2.85 to 8.72)	46	1.07 (0.79 to 1.46)	33	4.12 (2.74 to 6.19)	82	1.47 (1.16 to 1.86)
< 5	799 (4)	18	6.29 (3.50 to 11.30)	37	1.25 (0.89 to 1.76)	30	5.58 (3.64 to 8.53)	62	1.69 (1.29 to 2.20)
Recent smoker	4,059 (20)	178	14.68 (10.02 to 21.51)	152	1.14 (0.94 to 1.39)	144	6.12 (4.62 to 8.10)	308	2.10 (1.81 to 2.43)

NOTE. Of the 1,000 deaths not attributed to breast cancer, respiratory cancer, other cancer, noncancer respiratory disease, or cardiovascular disease, the two most common causes of death were diseases of the nervous system (ICD-9: 320-359; ICD-10: G00-G99), including Alzheimer and Parkinson diseases (n = 163 deaths), and mental and behavioral disorders (ICD-9: 290-319; ICD-10: F00-F99), including dementia (n = 149 deaths).

Abbreviations: HR, hazard ratio; ICD-9, International Classification of Diseases, ninth revision; ICD-10, International Classification of Diseases, tenth revision.

*Respiratory cancer includes neoplasms of the nasopharynx, larynx, trachea, bronchus, lung, pleura, and intrathoracic organs.

†Noncancer respiratory disease includes acute upper and lower respiratory infections/syndromes, influenza, pneumonia, bronchitis, emphysema, asthma, chronic obstructive pulmonary disease, and other respiratory disorders.

‡Cardiovascular disease includes rheumatic heart disease, hypertensive heart disease, ischemic heart disease, pulmonary heart disease, cerebrovascular disease, arterial/vascular diseases, embolism, thrombosis, and other disorders of the circulatory system.

§HR stratified by age at diagnosis, study phase, state of residence, and stage at diagnosis and adjusted for education, body mass index, parous status, age at first birth, menopausal status, use of postmenopausal hormone therapy, mammography history, alcohol consumption, and first-degree family history of breast cancer.

Table A3. Characteristics at Breast Cancer Diagnosis According to Cigarette Smoking Status After Diagnosis

Characteristic at diagnosis	No. (%) of Patients			
		By Cigarette Smoking Status After Diagnosis*		
	Total (N = 4,562)	Never (n = 2,219)	Former (n = 1,909)	Current (n = 434)
Age, years				
< 50	908 (20)	467 (21)	330 (17)	111 (26)
50-59	1,433 (31)	605 (27)	654 (34)	174 (40)
60-69	1,684 (37)	827 (37)	723 (38)	134 (31)
70-79	537 (12)	320 (14)	202 (11)	15 (3)
State of residence				
New Hampshire	442 (10)	196 (9)	196 (10)	50 (12)
Massachusetts	1,488 (33)	627 (28)	716 (38)	145 (33)
Wisconsin	2,632 (58)	1,396 (63)	997 (52)	239 (55)
Education				
Less than high school	390 (9)	203 (9)	147 (8)	40 (9)
High school or some college	3,036 (67)	1,450 (65)	1,266 (66)	320 (74)
College degree	734 (16)	353 (16)	323 (17)	58 (13)
Professional or graduate degree	398 (9)	212 (10)	170 (9)	16 (4)
Unknown	4 (—)	1 (—)	3 (—)	0 (—)
Body mass index, kg/m^2*				
< 18.5	66 (1)	24 (1)	28 (1)	14 (3)
18.5-24.9	2,310 (51)	1,095 (50)	981 (52)	234 (54)
25.0-29.9	1,411 (31)	691 (31)	581 (31)	139 (32)
≥ 30	744 (16)	393 (18)	306 (16)	45 (10)
Unknown	31 (—)	16 (—)	13 (—)	2 (—)
Parous				
No	569 (12)	283 (13)	223 (12)	63 (15)
Yes	3,987 (88)	1,931 (87)	1,686 (88)	370 (85)
Unknown	6 (—)	5 (—)	0 (—)	1 (—)
Age at first birth, years†				
< 20	549 (14)	241 (12)	234 (14)	74 (20)
20-24	1,935 (49)	923 (48)	827 (49)	185 (50)
25-29	1,084 (27)	562 (29)	445 (26)	77 (21)
≥ 30	417 (10)	204 (11)	180 (11)	33 (9)
Unknown	2 (—)	1 (—)	0 (—)	1 (—)
Postmenopausal*				
No	1,072 (25)	560 (26)	393 (22)	119 (29)
Yes	3,300 (75)	1,589 (74)	1,419 (78)	292 (71)
Unknown	190 (—)	70 (—)	97 (—)	23 (—)
Postmenopausal hormone use*‡				
Never	1,794 (60)	877 (61)	755 (58)	162 (61)
Former	281 (9)	143 (10)	121 (9)	17 (6)
Recent	928 (31)	415 (29)	427 (33)	86 (32)
Unknown	297 (—)	154 (—)	116 (—)	27 (—)
Recent alcohol consumer*				
No	728 (16)	417 (19)	247 (13)	64 (15)
Yes	3,822 (84)	1,795 (81)	1,658 (87)	369 (85)
Unknown	12 (—)	7 (—)	4 (—)	1 (—)
Alcoholic drinks/week*§				
≤ 2	2,269 (59)	1,269 (71)	826 (50)	174 (47)
3-6	755 (20)	295 (16)	385 (23)	75 (20)
7-9	403 (11)	140 (8)	217 (13)	46 (12)
≥ 10	395 (10)	91 (5)	230 (14)	74 (20)
Mammography in lifetime*				
No	715 (18)	336 (17)	296 (18)	83 (22)
Yes	3,243 (82)	1,599 (83)	1,348 (82)	296 (78)
Unknown	604 (—)	284 (—)	265 (—)	55 (—)
First-degree family history of breast cancer				
No	3,582 (80)	1,762 (80)	1,486 (79)	334 (80)
Yes	923 (20)	434 (20)	404 (21)	85 (20)
Unknown	57 (—)	23 (—)	19 (—)	15 (—)
Stage				
Localized	3,344 (73)	1,599 (72)	1,424 (75)	321 (74)
Regional	1,218 (27)	620 (28)	485 (25)	113 (26)

*As of 1 year before diagnosis.
†Among parous women.
‡Among postmenopausal women.
§Among recent alcohol consumers.

Table A4. Characteristics After Breast Cancer Diagnosis According to Cigarette Smoking Status After Diagnosis

Characteristic after diagnosis*	No. (%) of Patients			
		By Cigarette Smoking Status After Diagnosis*		
	Total (N = 4,562)	Never (n = 2,219)	Former (n = 1,909)	Current (n = 434)
Age, years				
< 50	463 (10)	251 (11)	160 (8)	52 (12)
50-59	1,110 (24)	487 (22)	478 (25)	145 (33)
60-69	1,506 (33)	677 (31)	681 (36)	148 (34)
≥ 70	1,483 (33)	804 (36)	590 (31)	89 (21)
Body mass index, kg/m^2				
< 18.5	64 (1)	25 (1)	23 (1)	16 (4)
18.5-24.9	1,663 (39)	803 (39)	682 (38)	178 (43)
25.0-29.9	1,493 (35)	700 (34)	658 (37)	135 (33)
≥ 30	1,077 (25)	556 (27)	437 (24)	84 (20)
Unknown	265 (—)	135 (—)	109 (—)	21 (—)
Postmenopausal				
No	217 (5)	121 (6)	72 (4)	24 (6)
Yes	3,797 (95)	1,839 (94)	1,609 (96)	349 (94)
Unknown	548 (—)	259 (—)	228 (—)	61 (—)
Postmenopausal hormone use†				
Never	1,966 (60)	972 (61)	812 (57)	182 (61)
Former	1,176 (36)	538 (34)	534 (38)	104 (35)
Current	153 (5)	72 (5)	70 (5)	11 (4)
Unknown	502 (—)	257 (—)	193 (—)	52 (—)
Current alcohol consumer				
No	1,059 (23)	607 (28)	356 (19)	96 (22)
Yes	3,466 (77)	1,593 (72)	1,537 (81)	336 (78)
Unknown	37 (—)	19 (—)	16 (—)	2 (—)
Alcoholic drinks/week‡				
≤ 2	2,083 (60)	1,125 (71)	794 (52)	164 (49)
3-6	724 (21)	295 (19)	362 (24)	67 (20)
7-9	287 (8)	86 (5)	163 (11)	38 (11)
≥ 10	372 (11)	87 (5)	218 (14)	67 (20)

*As of follow-up questionnaire.
†Among postmenopausal women.
‡Among current alcohol consumers.

Table A5. Association Between Cigarette Smoking Status Before and After Diagnosis and Death As a Result of Cancer and Noncancer Causes

Cigarette smoking variable before/after diagnosis	No. (%) of Patients (N = 4,562)	Respiratory Cancer*		Other Cancer		Noncancer Respiratory Disease†		Cardiovascular Disease‡	
		No. of Deaths (n = 58)	HR§ (95% CI)	No. of Deaths (n = 164)	HR§ (95% CI)	No. of Deaths (n = 75)	HR§ (95% CI)	No. of Deaths (n = 258)	HR§ (95% CI)
Smoking status									
Never/never	2,219 (49)	4	1 (Reference)	74	1 (Reference)	19	1 (Reference)	117	1 (Reference)
Former/former	1,557 (34)	18	7.82 (2.46 to 24.89)	65	1.28 (0.89 to 1.83)	29	3.65 (1.93 to 6.91)	84	1.58 (1.16 to 2.13)
Recent/former	352 (8)	10	23.49 (6.44 to 85.72)	16	1.71 (0.96 to 3.06)	14	9.93 (4.43 to 22.29)	28	3.17 (1.98 to 5.08)
Recent/current	434 (10)	26	60.80 (17.70 to 208.81)	9	0.83 (0.40 to 1.72)	13	9.17 (3.89 to 21.61)	29	3.98 (2.50 to 6.32)
Duration of smoking, years‖									
Never/never	2,219 (49)	4	1 (Reference)	74	1 (Reference)	19	1 (Reference)	117	1 (Reference)
Former/former									
< 30	1,135 (25)	6	3.50 (0.88 to 13.96)	40	1.17 (0.77 to 1.77)	11	2.36 (1.05 to 5.27)	41	1.34 (0.92 to 1.97)
≥ 30	422 (9)	12	16.78 (4.97 to 56.66)	25	1.41 (0.87 to 2.30)	18	5.49 (2.69 to 11.23)	43	1.88 (1.29 to 2.74)
Recent/former									
< 30	94 (2)	1	3.28 (0.26 to 41.78)	2	1.62 (0.39 to 6.74)	1	2.88 (0.06 to 135.68)	3	3.13 (0.88 to 11.16)
≥ 30	258 (6)	9	30.66 (8.30 to 113.25)	14	1.78 (0.97 to 3.28)	13	10.33 (4.58 to 23.30)	25	3.14 (1.93 to 5.12)
Recent/current									
< 30	111 (2)	0	—	3	1.89 (0.54 to 6.54)	1	2.54 (0.16 to 41.24)	12	3.28 (0.69 to 15.63)
≥ 30	323 (7)	26	78.78 (22.37 to 277.44)	6	0.66 (0.28 to 1.57)	12	10.03 (4.13 to 24.36)	17	4.03 (2.50 to 6.49)
Amount of smoking, pack-years‖									
Never/never	2,219 (49)	4	1 (Reference)	74	1 (Reference)	19	1 (Reference)	117	1 (Reference)
Former/former									
< 30	1,205 (26)	7	4.22 (1.16 to 15.30)	46	1.19 (0.80 to 1.77)	15	2.64 (1.27 to 5.49)	62	1.56 (1.12 to 2.17)
≥ 30	352 (8)	11	21.63 (6.06 to 77.23)	19	1.60 (0.93 to 2.74)	14	6.82 (3.05 to 15.27)	22	1.64 (1.00 to 2.67)
Recent/former									
< 30	168 (4)	4	16.06 (2.46 to 104.75)	6	1.41 (0.59 to 3.37)	2	3.46 (0.51 to 23.28)	13	3.26 (1.70 to 6.26)
≥ 30	184 (4)	6	29.87 (7.75 to 115.18)	10	2.00 (0.98 to 4.07)	12	12.61 (5.38 to 29.56)	15	3.11 (1.71 to 5.65)
Recent/current									
< 30	183 (4)	6	31.59 (7.22 to 138.25)	2	0.47 (0.11 to 1.95)	2	2.50 (0.47 to 13.21)	11	3.74 (1.91 to 7.34)
≥ 30	251 (6)	20	92.81 (25.19 to 341.88)	7	1.09 (0.48 to 2.49)	11	14.98 (5.94 to 37.78)	18	4.15 (2.37 to 7.28)

NOTE. Of the 1,000 deaths not attributed to breast cancer, respiratory cancer, other cancer, noncancer respiratory disease, or cardiovascular disease, the two most common causes of death were diseases of the nervous system (ICD-9: 320-359; ICD-10: G00-G99), including Alzheimer and Parkinson diseases (n = 163 deaths), and mental and behavioral disorders (ICD-9: 290-319; ICD-10: F00-F99), including dementia (n = 149 deaths).

Abbreviations: HR, hazard ratio; ICD-9, International Classification of Diseases, ninth revision; ICD-10, International Classification of Diseases, tenth revision.

*Respiratory cancer includes neoplasms of the nasopharynx, larynx, trachea, bronchus, lung, pleura, and intrathoracic organs.

†Noncancer respiratory disease includes acute upper and lower respiratory infections/syndromes, influenza, pneumonia, bronchitis, emphysema, asthma, chronic obstructive pulmonary disease, and other respiratory disorders.

‡Cardiovascular disease includes rheumatic heart disease, hypertensive heart disease, ischemic heart disease, pulmonary heart disease, cerebrovascular disease, arterial/vascular diseases, embolism, thrombosis, and other disorders of the circulatory system.

§HR stratified by age at diagnosis, study phase, state of residence, and stage at diagnosis and adjusted for education, body mass index, parous status, age at first birth, menopausal status, use of postmenopausal hormone therapy, mammography history, alcohol consumption, first-degree family history of breast cancer, postdiagnosis body mass index, postdiagnosis alcohol consumption, and time from diagnosis to post-diagnosis questionnaire.

‖Duration and pack-years calculated for smoking before diagnosis.