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Health-related behaviors and mortality outcomes in women diagnosed with ductal carcinoma in situ

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Abstract
Purpose Women diagnosed with ductal carcinoma in situ (DCIS) of the breast are at greater risk of dying from cardiovascular disease and other causes than from breast cancer, yet associations between health-related behaviors and mortality outcomes after DCIS have not been well studied.
Methods We examined the association of body mass index, physical activity, alcohol consumption, and smoking with mortality among 1925 women with DCIS in the Wisconsin In Situ Cohort study. Behaviors were self-reported through baseline interviews and up to three follow-up questionnaires. Cox proportional hazards regression was used to estimate hazard ratios (HR) and 95% confidence intervals (CI) for mortality after DCIS, with adjustment for patient sociodemographic, comorbidity, and treatment factors.
Results Over a mean of 6.7 years of follow-up, 196 deaths occurred. All-cause mortality was elevated among women who were current smokers 1 year prior to diagnosis (HR = 2.17 [95% CI 1.48, 3.18] vs. never smokers) and reduced among women with greater physical activity levels prior to diagnosis (HR = 0.55 [95% CI: 0.35, 0.87] for ≥5 h per week vs. no activity). Moderate levels of post-diagnosis physical activity were associated with reduced all-cause mortality (HR = 0.31 [95% CI 0.14, 0.68] for 2–5 h per week vs. no activity). Cancer-specific mortality was elevated among smokers and cardiovascular disease mortality decreased with increasing physical activity levels.
Conclusions There are numerous associations between health-related behaviors and mortality outcomes after a DCIS diagnosis.
Implications for cancer survivors Women diagnosed with DCIS should be aware that their health-related behaviors are associated with mortality outcomes.

Keywords Breast neoplasms · Non-infiltrating intra-ductal carcinoma · Health behavior · Cause of death · Follow-up studies

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Introduction

Ductal carcinoma in situ (DCIS) is a non-invasive breast cancer in which malignant cells are confined within the basement membrane of the breast duct [1]. Before the use of screening mammography became common, a DCIS diagnosis was relatively rare [2]. However, as routine screening became more common since the 1980s and screening methods became more sensitive, the incidence of DCIS has greatly increased.

Currently in the USA, DCIS comprises approximately 20% of new breast cancer diagnoses and impacts over 60,000 women each year [3]. Approximately one million women are estimated to be living with a DCIS diagnosis in the USA [4].

As the number of DCIS cases continues to increase, more research on survivorship in this population is needed. Women diagnosed with DCIS have a high survival rate compared to women diagnosed with other stages of breast cancer [5] and are at greater risk of dying from cardiovascular disease (CVD) and other causes than from breast cancer [2, 6]. A DCIS diagnosis is frequently followed by adverse changes in health-related behaviors, including decreased physical activity and weight gain [7–10]. These changes are likely due to the physical and psychological impacts of DCIS diagnosis and treatment, which typically includes surgery and radiation, often combined with endocrine therapy [11]. Thus, the promotion of healthy behaviors that influence a variety of outcomes after diagnosis may warrant increased attention during DCIS management [11].

The role of health-related behaviors in promoting enhanced DCIS survivorship is not well understood. Smoking, physical inactivity, and excessive alcohol consumption have been associated with increased morbidity and mortality from the most common diseases in the general population [12–18]. Sedentary behavior and obesity place individuals at elevated risk of multiple chronic diseases such as diabetes, hypertension, osteoarthritis, coronary heart disease, and cancer [18–23] and are associated with increased risk for all-cause mortality [21, 24, 25]. Studies of invasive breast cancer survivors have found that obesity, physical inactivity, excessive alcohol consumption, and smoking are associated with elevated all-cause and breast cancer-specific mortality [26–30]. To our knowledge, no studies have examined how specific health behaviors are associated with mortality outcomes in women with a DCIS diagnosis.

We evaluated the association of specific health-related behaviors with all-cause, cancer-specific, and CVD-specific mortality among women with DCIS using data from the Wisconsin In Situ Cohort (WISC). We hypothesized that the maintenance or adoption of healthy behaviors, including regular physical activity, avoidance of smoking, moderate alcohol consumption, and maintaining a healthy BMI, would be associated with lower mortality rates overall—from non-cancer as well as cancer causes.

Methods

Study population

As previously described [7, 10], the WISC study consists of 1925 women with an incident primary DCIS diagnosis reported to the Wisconsin Cancer Reporting System (the mandatory statewide tumor registry) between 1997 and 2006. Eligibility criteria for enrollment into the WISC study included a known date of diagnosis, a listed telephone number, and the ability to participate in a telephone interview. Women included in this cohort were Wisconsin residents between the ages of 20 and 74 at their initial diagnosis. A total of 1925 women with DCIS were enrolled between 1997 and 2006.

Data collection

Baseline and follow-up questionnaires were administered to the cohort to collect health behavior, demographic, reproductive, and medical history data. The baseline questionnaire was conducted via a telephone interview (median 1.3 years after DCIS diagnosis), with 76% of eligible women participating. Beginning in 2003, biennial follow-up questionnaires were administered by telephone (2003–2006) or via mailed surveys (2010–2011). Of the women eligible for re-contact, 78% participated in the first re-contact telephone interview (2003–2006), 86% participated in the second interview (2005–2006), and 73% participated in the third re-contact mailed survey (2010–2011).

Health-related behaviors

Collection of health-related behaviors in the WISC study has been previously described [10]. During the baseline interview, participants recalled their body weight, height, recreational physical activity, alcohol consumption, and smoking habits in the 1 year prior to their DCIS diagnosis. Current body weight and height and current smoking status were also reported at the baseline interview. Current status of all exposure variables were subsequently reported at each re-contact interview or survey. Each participant's reported body weight and height were used to calculate their body mass index (BMI) at each collection period.

Physical activity was assessed through questions patterned on the Nurses' Health Study [31]. Participants were asked to report their participation in regular physical activity, defined as at least 30 min per week for at least 3 months of the year. Respondents were prompted with specific categories of physical activity including swimming, jogging/running, bicycling, calisthenics/ aerobics/ dance, racquet sports, and walking/ hiking for exercise, and also invited to report other individual and team activities as an open-ended response option. Participants reported the number of months per year and hours per week spent performing each activity.

At the baseline interview, participants were asked to recall the number of bottles or cans of beer, glasses of wine, and drinks of hard liquor consumed per day, week, or month at 1 year prior to diagnosis. This information was combined to create a variable representing the total number of alcoholic drinks per week. At each re-contact interview, participants

reported typical alcohol consumption for the previous 12 months.

At the baseline interview, participants were asked whether they had smoked more than 100 cigarettes in their lifetime. Those that had were asked about their smoking status at 1 year prior to diagnosis and were classified as former or current smokers at that time. Current smoking status was collected at the baseline and subsequent follow-up interviews, and participants were classified as current, former, or never smokers based on their response and self-reported smoking status at previous interviews.

Other risk factors

During the baseline telephone interview, participants provided information on sociodemographics, and reproductive and medical history, as previously described [32]. Age at diagnosis, year of diagnosis, family history of breast cancer, education level, surgical treatment type, and post-treatment endocrine therapy use (tamoxifen, raloxifene, or aromatase inhibitors) were assessed at baseline and considered static in our analysis. Post-menopausal hormone use and comorbidity information were collected at each re-contact and considered time-varying in our analysis. The number of comorbidities was calculated based on diagnoses included in the Charlson Comorbidity Index [33].

Outcomes

Vital status and cause of death were determined via linkage with records complete through 2012 from the National Death Index. Underlying cause of death was assigned according to the International Classification of Diseases (ICD) tenth revision and classified as death due to cancer, cardiovascular disease, or other causes based on ICD codes as in our prior study [6]. Deaths caused by cancer included malignant neoplasms at all sites (C00-C97). Deaths caused by cardiovascular disease (CVD) included the following: diseases of the heart (I00–I09, I11, I13, I20–I51), cerebrovascular diseases (I60–I69), atherosclerosis (I70), and other diseases of arteries, arterioles, and capillaries (I72–I78).

Statistical analysis

The characteristics of the study population were examined overall. Multiple imputation [$N = 10$] was used to conduct analyses accounting for missing data [34]. The imputation model included all covariates listed above, as well as socioeconomic characteristics (income, insurance status, and living situation at baseline) and tumor and screening characteristics (size, grade, and number of mammograms in the past 5 years).

Multivariable-adjusted hazard ratios (HR) and 95% confidence intervals for the association between post-diagnosis health behaviors and mortality were estimated using Cox proportional hazard regression. Separate models were created for three primary outcomes of interest (all-cause mortality, cancer-specific mortality, and CVD-specific mortality) for each behavioral exposure. Follow-up time was defined as the time from initial DCIS diagnosis until the date of death or until December 31, 2012.

We investigated both pre-diagnosis and post-diagnosis behaviors in relation to mortality. The association with pre-diagnosis behavior was assessed using behavior information recalled at the baseline interview for 1 year prior to diagnosis. This analysis adjusted for all baseline covariates listed above.

To consider multiple post-diagnosis data points, a repeated measures analysis was performed to determine the association between post-diagnosis behavior levels and mortality. Behavior levels were treated as time varying and updated with the most recent values during the survival analysis. The post-diagnosis analyses adjusted for all covariates listed above. Two sets of models were used to produce results with or without adjustment for pre-diagnosis levels of the relevant behavior. At the baseline interview, women reported their current BMI and smoking status in addition to recalling BMI and smoking status for 1 year prior to diagnosis. Therefore, the post-diagnosis analysis for BMI and smoking included data from baseline and each of the three re-contact interviews, and included all death data. In contrast, at the baseline interview women recalled their physical activity and alcohol consumption at 1 year prior to diagnosis but did not report their current physical activity and alcohol consumption. Therefore the post-diagnosis analysis for physical activity and alcohol consumption only included data from the three re-contact interviews. As a result, deaths that occurred before the first re-contact interview ($N = 87$) were not included in the post-diagnosis analysis for these behaviors.

All statistical analysis was performed using SAS statistical software Version 9.2 (SAS Institute Inc., Cary, NC).

Results

Over a mean of 6.7 years of follow-up, 196 deaths were reported, including 87 cancer deaths, 34 CVD deaths, and 75 deaths due to other causes. Approximately 29% of participants had a college degree, and 31% had at least one comorbidity at the time of their DCIS diagnosis (Table 1).

All-cause mortality

A lower rate of all-cause mortality was observed in women that had a pre-diagnosis BMI between 25 and 30 kg/m^2 (HR 0.64, 95% CI 0.44–0.95) compared to women with a normal/

Table 1 Baseline characteristics of Wisconsin In Situ Cohort study participants with a diagnosis of ductal carcinoma in situ ($N = 1925$), 1997–2012

	N^a (%)
Age at diagnosis (years)	
20–44	237 (12.3)
45–54	686 (35.6)
55–64	584 (30.3)
65–74	418 (21.7)
Education	
<High school diploma	95 (4.9)
High school diploma	750 (39.0)
Some college	526 (27.3)
College degree	554 (28.8)
Surgical treatment	
Ipsilateral mastectomy	643 (33.4)
Bilateral mastectomy	134 (7.0)
BCS no radiation	232 (12.1)
BCS with radiation	859 (44.6)
Biopsy only	57 (3.0)
Family history of breast cancer	
No	1489 (77.4)
Yes	436 (22.6)
Adjuvant endocrine therapy use	
No	1171 (60.8)
Yes	754 (39.2)
Comorbidity status	
None	1326 (68.9)
One	395 (20.5)
Two	163 (8.5)
Three or more	41 (2.1)

BCS breast conserving surgery

[a] Missing values estimated using multiple imputation; category frequencies based on the mode of the ten imputations

healthy BMI (18.5–24.9 kg/m^2) (Table 2). Women that participated in more than 5 h per week of physical activity in the 1 year prior to diagnosis had approximately half the hazard ratio of sedentary women (HR 0.55, 95% CI 0.35–0.87). There was no evidence for an association between pre-diagnosis alcohol consumption and all-cause mortality. Women who were current smokers at 1 year prior to their DCIS diagnosis had more than double the hazard ratio of non-smokers (HR 2.17, 95% CI 1.48–3.18).

Post-diagnosis BMI was not significantly associated with all-cause mortality (Table 2). Modest levels of physical activity after diagnosis were associated with reduced all-cause mortality, even after adjusting for pre-diagnosis activity levels (HR = 0.31; 95% CI 0.14–0.68 for 2–5 h per week compared to no activity). All-cause mortality was elevated with increasing post-diagnosis alcohol consumption (HR = 1.04; 95% CI 1.01, 1.07 per each unit increase in drinks per week), though there was not a clear pattern in risk among the alcohol consumption categories examined. Post-diagnosis smoking was associated with all-cause mortality (HR = 2.29; 95% CI 1.50–3.50), though the association was attenuated and not statistically significant after adjusting for pre-diagnosis smoking status (HR = 1.49; 95% CI 0.70, 3.15).

Cancer-specific mortality

There was no evidence for an association between pre-diagnosis BMI, physical activity, or alcohol consumption and cancer-specific mortality (Table 3). However, cancer-specific mortality was elevated among women who were current smokers at 1 year prior to their DCIS diagnosis (HR 2.00, 95% CI 1.14–3.50).

Neither post-diagnosis BMI nor physical activity was associated with cancer-specific mortality. We observed an association between post-diagnosis alcohol consumption and cancer-specific mortality, but again only when alcohol consumption was treated as a continuous variable (HR = 1.04; 95% CI 1.00, 1.08 per unit increase in drinks per week). Post-diagnosis smoking was associated with elevated cancer-specific mortality (HR = 2.59; 95% CI 1.43, 4.70); the hazard ratio remained elevated after adjusting for pre-diagnosis smoking but was no longer statistically significant (HR = 2.88; 95% CI 0.88, 9.44).

Cardiovascular disease mortality

Pre-diagnosis BMI and alcohol consumption were not associated with CVD-specific mortality (Table 4). There were some evidence that CVD-specific mortality was lower among women with elevated pre-diagnosis physical activity levels (HR = 0.83; 95% CI 0.70, 0.98 per 1 h/wk increase in activity) and higher among women who were current smokers prior to their diagnosis, though the hazard ratio for smoking failed to reach statistical significance (HR = 2.07; 95% CI 0.84, 5.11). There was no evidence for independent associations between post-diagnosis behaviors and CVD-specific mortality.

Discussion

In this cohort, we found numerous associations between health-related behaviors and mortality outcomes after a DCIS diagnosis. This evidence is newly reported and was strongest for smoking, which was associated with all-cause and cancer-specific mortality, and physical activity, which was associated with all-cause and CVD-specific mortality. These findings demonstrate the importance of health-related behaviors in outcomes after a DCIS diagnosis.

These finding are supported by some, but not all, results of studies in women following a diagnosis of invasive breast cancer. We observed that smoking status at 1 year prior to

Table 2 Hazard ratios and 95% confidence intervals for the association of health behaviors with risk of all-cause mortality after a diagnosis of ductal carcinoma in situ; Wisconsin In Situ Cohort study, 1997–2012

	Pre-diagnosis behaviors	Post-diagnosis behaviors	
	HR (95% CI)[a]	HR (95% CI)[b]	HR (95% CI)[c]
Body mass index (kg/m^2)			
18.5–24.9	1 (ref)	1 (ref)	1 (ref)
25.0–29.9	*0.64 (0.44, 0.95)*	0.75 (0.51, 1.11)	0.79 (0.51, 1.24)
30.0–34.9	0.78 (0.50, 1.21)	0.79 (0.49, 1.25)	0.89 (0.47, 1.70)
35.0+	1.06 (0.62, 1.81)	1.24 (0.76, 2.02)	1.48 (0.69, 3.19)
Continuous unit increase	0.99 (0.96, 1.02)	1.00 (0.98, 1.03)	1.02 (0.98, 1.07)
Physical activity (hours per week)			
No activity	1 (ref)	1 (ref)	1 (ref)
0–1.9	*0.63 (0.43, 0.94)*	*0.48 (0.25, 0.91)*	0.53 (0.27, 1.01)
2.0–4.9	*0.63 (0.43, 0.92)*	*0.27 (0.12, 0.59)*	*0.31 (0.14, 0.68)*
5.0+	*0.55 (0.35, 0.87)*	0.65 (0.30, 1.42)	0.85 (0.38, 1.91)
Continuous unit increase	0.97 (0.94, 1.02)	0.95 (0.88, 1.04)	0.97 (0.90, 1.06)
Alcohol (drinks per week)			
Non-drinker	1 (ref)	1 (ref)	1 (ref)
0–1.9	0.81 (0.56, 1.17)	0.83 (0.51, 1.33)	0.82 (0.50, 1.34)
2.0–6.9	0.80 (0.51, 1.27)	0.76 (0.40, 1.44)	0.74 (0.36, 1.50)
7.0+	0.82 (0.50, 1.34)	1.09 (0.59, 2.00)	1.03 (0.47, 2.27)
Continuous unit increase	1.00 (0.97, 1.03)	*1.03 (1.01, 1.06)*	*1.04 (1.01, 1.07)*
Smoking			
Non-smoker	1 (ref)	1 (ref)	1 (ref)
Former smoker	1.04 (0.73, 1.48)	1.06 (0.76, 1.49)	1.00 (0.70, 1.42)
Current smoker	*2.17 (1.48, 3.18)*	*2.29 (1.50, 3.50)*	1.49 (0.70, 3.15)

Italic emphasis is used to identify statistically significant findings

[a] Adjusted for age at diagnosis, family history of breast cancer, education at baseline, surgical treatment type, year of diagnosis, post-treatment endocrine therapy use, and pre-diagnosis values of remaining exposures as static covariates; adjusted for number of comorbidities and post-menopausal hormone use as time-varying covariates

[b] No adjustment for pre-diagnosis behaviors. Adjusted for age at diagnosis, family history of breast cancer, education at baseline, surgical treatment type, year of diagnosis, post-treatment endocrine therapy use; adjusted for number of comorbidities, post-menopausal hormone use, and remaining exposures as time-varying covariates

[c] Adjusted for pre-diagnosis exposure level as static covariates, in addition to all variables listed in footnote b

diagnosis was associated with an increased all-cause, cancer-specific, and CVD-specific mortality after DCIS (though the latter association was not statistically significant). This is consistent with other studies evaluating smoking behavior and invasive breast cancer survival [28–30, 35, 36]. We found that post-diagnosis smoking was also associated with elevated mortality outcomes, though the results were attenuated and not statistically significant after adjusting for pre-diagnosis smoking status. A large, prospective cohort study of women with invasive breast cancer previously reported that, compared to never smokers, women who were current smokers after diagnosis had an almost fourfold higher rate of dying from causes other than breast cancer (HR = 3.84, 95% CI 2.50–5.89) [30]. However, it is unclear if this study adjusted for pre-diagnosis smoking status in their analyses. Notably our results for post-diagnosis smoking status have wide confidence intervals due to the relatively small numbers of post-diagnosis smokers.

In a meta-analysis of six studies examining physical activity and survival after a breast cancer diagnosis, Ibrahim et al. found increasing hours of physical activity, both pre and post-diagnosis, reduced overall mortality risk (pre-diagnosis HR = 0.82, 95% CI 0.67–0.99; post-diagnosis HR = 0.59, 95% CI 0.53–0.65) [37]. A subsequent meta-analysis performed by Zhong et al. included ten additional cohort studies and further suggested that women participating in moderate to high levels of pre- and post- diagnosis physical activity were at a reduced risk of all-cause mortality compared to women with little to no participation in physical activity (pre-diagnosis: RR = 0.79, 95% CI 0.73–0.85; post-diagnosis RR = 0.57, 95% CI 0.45–0.72) [38].

Prior studies indicate that pre- and post-diagnosis obesity are associated with increased all-cause mortality among invasive breast cancer survivors [27, 39–42]. In a meta-analysis of 82 studies of breast cancer survivors with BMI measurements before and after diagnosis, Chan et al. found obese patients

Table 3 Hazard ratios and 95% confidence intervals for the association of health behaviors and the risk of cancer mortality after a diagnosis of ductal carcinoma in situ; Wisconsin In Situ Cohort study, 1997–2012

	Pre-diagnosis behaviors	Post-diagnosis behaviors	
	HR (95% CI)[a]	HR (95% CI)[b]	HR (95% CI)[c]
Body mass index (kg/m^2)			
18.5–24.9	1 (ref)	1 (ref)	1 (ref)
25.0–29.9	0.77 (0.46, 1.29)	0.70 (0.39, 1.25)	0.75 (0.39, 1.43)
30.0–34.9	0.71 (0.35, 1.44)	0.72 (0.36, 1.43)	0.84 (0.34, 2.06)
35.0+	1.10 (0.47, 2.56)	1.34 (0.66, 2.73)	1.68 (0.56, 5.01)
Continuous unit increase	0.99 (0.95, 1.04)	1.00 (0.96, 1.04)	1.01 (0.94, 1.08)
Physical activity (hours per week)			
No activity	1 (ref)	1 (ref)	1 (ref)
0–1.9	0.62 (0.33, 1.15)	0.48 (0.19, 1.27)	0.55 (0.21, 1.45)
2.0–4.9	0.87 (0.51, 1.48)	*0.34 (0.12, 0.97)*	0.38 (0.13, 1.10)
5.0+	0.59 (0.29, 1.18)	0.73 (0.25, 2.16)	0.92 (0.30, 2.86)
Continuous unit increase	1.01 (0.96, 1.06)	0.99 (0.89, 1.09)	1.00 (0.89, 1.11)
Alcohol (drinks per week)			
Non-drinker	1 (ref)	1 (ref)	1 (ref)
0–1.9	0.83 (0.47, 1.46)	0.70 (0.36, 1.37)	0.69 (0.35, 1.38)
2.0–6.9	0.65 (0.31, 1.36)	0.41 (0.15, 1.15)	0.39 (0.13, 1.21)
7.0+	1.32 (0.66, 2.64)	0.97 (0.43, 2.20)	0.91 (0.32, 2.61)
Continuous unit increase	1.02 (0.98, 1.07)	*1.04 (1.01, 1.07)*	*1.04 (1.00, 1.08)*
Smoking			
Non-smoker	1 (ref)	1 (ref)	1 (ref)
Former smoker	1.02 (0.61, 1.70)	0.96 (0.58, 1.58)	0.97 (0.58, 1.63)
Current smoker	*2.00 (1.14, 3.50)*	*2.59 (1.43, 4.70)*	2.88 (0.88, 9.44)

Italic emphasis is used to identify statistically significant findings

[a] Adjusted for age at diagnosis, family history of breast cancer, education at baseline, surgical treatment type, year of diagnosis, post-treatment endocrine therapy use, and pre-diagnosis values of remaining exposures as static covariates; adjusted for number of comorbidities and post-menopausal hormone use as time-varying covariates

[b] No adjustment for pre-diagnosis behaviors. Adjusted for age at diagnosis, family history of breast cancer, education at baseline, surgical treatment type, year of diagnosis, post-treatment endocrine therapy use; adjusted for number of comorbidities, post-menopausal hormone use, and remaining exposures as time-varying covariates

[c] Adjusted for pre-diagnosis exposure level as static covariates, in addition to all variables listed in footnote b

had modestly increased mortality rates than normal weight patients, regardless of when BMI was ascertained (measured at pre-diagnosis: RR = 1.41, 95% CI 1.29,1.53; measured ≥12 months after diagnosis: RR = 1.21, 95% CI 1.06–1.38) [42]. We detected no association between pre- or post-diagnosis obesity and mortality outcomes. However, women who were overweight (25–30 kg/m^2) prior to diagnosis had reduced all-cause mortality compared to normal weight women. This finding is consistent with prior studies reporting lower mortality among overweight individuals compared to normal weight individuals in the general population, perhaps due to an increased ability to survive infections and other illnesses [43–45]. However, this result should be interpreted with caution given known challenges in evaluating the relationship between body weight and mortality outcomes, which can most notably be confounded by unintentional weight loss due to underlying disease during the period preceding the collection of weight data [46]. Nevertheless, our results suggest that in this regard DCIS survivors may be more similar to the general population than to invasive breast cancer survivors.

Two large studies of invasive breast cancer survivors found that moderate alcohol intake was associated with 15–30% reductions in the all-cause mortality rate [47, 48]. In contrast, we found that post-diagnosis alcohol consumption had a modest positive association with all-cause and cancer-specific mortality, but only when alcohol consumption was modeled as a continuous variable. The lack of association between our categorical alcohol variables and mortality outcomes, and an inspection of the distribution of alcohol consumption in the cohort suggest that the observed association is largely due to outliers with high alcohol consumption (e.g., more than 25 drinks per week).

Important strengths of this study include the large, population-based cohort of DCIS survivors and the collection of up to 11 years of health behavior data following initial diagnosis. Furthermore, our prospective study design allowed

Table 4 Hazard ratios and 95% confidence intervals for the association of health behaviors and the risk of cardiovascular disease mortality after a diagnosis of ductal carcinoma in situ; Wisconsin In Situ Cohort study, 1997–2012

	Pre-diagnosis behaviors	Post-diagnosis behaviors	
	HR (95% CI)[a]	HR (95% CI)[b]	HR (95% CI)[c]
Body mass index (kg/m^2)			
18.5–24.9	1 (ref)	1 (ref)	1 (ref)
25.0–29.9	0.88 (0.37, 2.07)	1.32 (0.53, 3.27)	0.90 (0.32, 2.51)
30.0–34.9	1.21 (0.45, 3.24)	1.44 (0.51, 4.09)	0.63 (0.15, 2.70)
35.0+	1.85 (0.59, 5.85)	1.18 (0.30, 4.68)	0.36 (0.05, 2.74)
Continuous unit increase	1.01 (0.95, 1.07)	1.01 (0.95, 1.07)	0.96 (0.85, 1.08)
Physical activity (hours per week)			
No activity	1 (ref)	1 (ref)	1 (ref)
0–1.9	0.52 (0.22, 1.23)	0.29 (0.04, 2.41)	0.35 (0.04, 2.97)
2.0–4.9	*0.38 (0.15, 1.00)*	0.29 (0.03, 2.36)	0.42 (0.05, 3.60)
5.0+	0.29 (0.08, 1.04)	1.38 (0.29, 6.50)	2.27 (0.40, 12.76)
Continuous unit increase	*0.83 (0.70, 0.98)*	1.01 (0.90, 1.14)	1.04 (0.91, 1.18)
Alcohol (drinks per week)			
Non-drinker	1 (ref)	1 (ref)	1 (ref)
0–1.9	0.68 (0.29, 1.60)	1.39 (0.39, 4.98)	1.43 (0.37, 5.62)
2.0–6.9	1.22 (0.47, 3.14)	1.43 (0.28, 7.21)	1.53 (0.24, 9.89)
7.0+	0.49 (0.13, 1.86)	0.51 (0.05, 4.84)	0.57 (0.04, 8.52)
Continuous unit increase	1.01 (0.94, 1.08)	0.87 (0.66, 1.16)	0.90 (0.67, 1.22)
Smoking			
Non-smoker	1 (ref)	1 (ref)	1 (ref)
Former smoker	0.96 (0.43, 2.15)	1.00 (0.47, 2.17)	0.92 (0.41, 2.08)
Current smoker	2.07 (0.84, 5.11)	2.32 (0.87, 6.13)	1.27 (0.22, 6.86)

Italic emphasis is used to identify statistically significant findings

[a] Adjusted for age at diagnosis, family history of breast cancer, education at baseline, surgical treatment type, year of diagnosis, post-treatment endocrine therapy use, and pre-diagnosis values of remaining exposures as static covariates; adjusted for number of comorbidities and post-menopausal hormone use as time-varying covariates

[b] No adjustment for pre-diagnosis behaviors. Adjusted for age at diagnosis, family history of breast cancer, education at baseline, surgical treatment type, year of diagnosis, post-treatment endocrine therapy use; adjusted for number of comorbidities, post-menopausal hormone use, and remaining exposures as time-varying covariates

[c] Adjusted for pre-diagnosis exposure level as static covariates, in addition to all variables listed in footnote b

us to measure exposures at multiple time points to reflect changes in health behaviors over time following the DCIS diagnosis.

There are several limitations that should be considered while interpreting the results of this study. Participants in this study self-reported all health-behavior information. While sub-studies of this cohort have reported good reliability for reports of body weight and alcohol consumption (intra-class correlation coefficient >0.75) [7], the accuracy of recalled behaviors was not assessed in this population. Baseline interviews were conducted a median of 1.3 years after diagnosis; thus, a majority of women reporting their behaviors for 1 year prior to diagnosis had to recall behaviors from more than 2 years prior. Non-differential misclassification due to errors in recall would tend to attenuate the observed associations. Thus, our study may underestimate the associations between pre-diagnosis behaviors and mortality outcomes. Despite high participation rates during WISC follow-up, non-response at each data collection period may also have affected our results. Finally, the WISC study includes one of the largest DCIS cohorts with extended follow-up data, yet the sample size was nonetheless insufficient to detect modest differences in mortality rates.

As the DCIS survivor population continues to grow, more research needs to be conducted on interventions and survivorship outcomes within this population. Our study suggests a woman's smoking status and physical activity are associated with mortality outcomes after a DCIS diagnosis. These results demonstrate the importance of maintaining healthy behaviors and provide additional support to clinicians when promoting healthy behaviors to DCIS survivors. Future studies with large sample sizes are needed to establish the consistency of these results.

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Compliance with ethical standards

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Conflict of interest All authors report no conflicts of interest.

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

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