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EPIDEMIOLOGY

Impact of very low physical activity, BMI, and comorbidities on mortality among breast cancer survivors

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Abstract The purpose of this study was to examine post-diagnosis BMI, very low physical activity, and comorbidities, as predictors of breast cancer-specific and all-cause mortality. Data from three female US breast cancer survivor cohorts were harmonized in the After Breast Cancer Pooling Project ($n = 9513$). Delayed entry Cox proportional hazards models were used to examine the impact of three post-diagnosis lifestyle factors: body mass index (BMI), select comorbidities (diabetes only, hypertension only, or both), and very low physical activity (defined as physical activity <1.5 MET h/week) in individual models and together in multivariate models for breast cancer and all-cause mortality. For breast cancer mortality, the individual lifestyle models demonstrated a significant association with very low physical activity but not with the selected comorbidities or BMI. In the model that included all three lifestyle variables, very low physical activity was associated with a 22 % increased risk of breast cancer mortality (HR 1.22, 95 % CI 1.05, 1.42). For all-cause mortality, the three individual models demonstrated significant associations for all three lifestyle predictors. In the combined model, the strength and significance of the association of comorbidities (both hypertension and diabetes versus neither: HR 2.16, 95 % CI 1.79, 2.60) and very low physical activity (HR 1.35, 95 % CI 1.22, 1.51) remained unchanged, but the association with obesity was completely attenuated. These data indicate that after active treatment, very low physical activity, consistent with a sedentary lifestyle (and comorbidities for all-cause mortality), may account for the increased risk of mortality, with higher BMI, that is seen in other studies.

Keywords Sedentary behavior · Lifestyle factors · Diabetes · Obesity · Body mass index

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Introduction

The large (3.1 million) and growing population of breast cancer survivors in the US [1] emphasizes the importance of interventions to improve survival. One area of concern is the major epidemic of obesity that is occurring in the US [2]. Adult obesity is associated with an increased risk for many diseases, including diabetes, cardiovascular disease, and numerous cancers, including the development of breast cancer. However, the role of obesity in breast cancer survivorship is less clear.

The American Society of Clinical Oncology (ASCO) and the World Cancer Research Fund recently released

position statements with differing conclusions regarding the role of obesity in cancer. ASCO concluded that obesity is a major unrecognized risk factor for cancer and is associated with worsened prognosis after cancer diagnosis [3]. While the World Cancer Research Fund report concluded that obesity was associated with an increased risk of developing breast cancer, there was limited evidence that greater body fatness increases risk of breast cancer-specific mortality.

There are numerous potential explanations for the conflicting data on the association of obesity with breast cancer prognosis. In particular, many factors are correlated with weight status and breast cancer risk, and failure to account for them may obscure the true risk of excess weight. A recent re-analysis of NHANES data demonstrated the dramatic effects that this source of bias had on estimates of obesity-associated deaths [4]. Specifically, models that failed to account for the confounding effects of age, sex, and lifestyle (tobacco and alcohol) overestimated obesity-associated deaths by upwards of 30 %: an inflation of more than 100,000 deaths.

The objective of this study was to examine associations of post-diagnosis body mass index (BMI) with breast cancer-specific and all-cause mortality before and after adjustment for 2 major factors associated with weight and breast cancer: select comorbidities [5] and very low physical activity, consistent with a sedentary lifestyle [6, 7]. Data from a large, well-characterized, diverse cohort of US breast cancer survivors, comprising the After Breast Cancer Pooling Project, were used to examine the hypothesis that the combination of high BMI, very low physical activity, and select comorbidities, when modeled together, would provide insight into the independent association of post-diagnosis BMI with breast cancer-specific and all-cause mortality.

Methods

Study population

The details of the ABCPP have been described previously [8]. For this analysis, the three US cohorts included in the ABCPP were the women's healthy eating and living (WHEL) study [9], the life after cancer epidemiology (LACE) study [10], and the nurses' health study (NHS) [11].

Dates of original breast cancer diagnosis ranged from 1976 to 2006 in the ABCPP. We excluded women who were diagnosed before 1991 ($n = 3084$) because this was before adjuvant endocrine therapy became standard of care, who had stage IV tumors at diagnosis ($n = 126$), who were missing data for physical activity ($n = 292$) or BMI ($n = 459$), or who had self-reported prevalent CVD only, as described below in descriptor of comorbidities, ($n = 84$); leaving an analytical sample size of 9513. Data from the three cohorts were harmonized, as described previously [8]. Institutional review board approval was obtained for each cohort study.

Data collection

Body mass index

Baseline body mass index (BMI) was obtained a mean of 1.4 years post-diagnosis. BMI was calculated from a weight and height that was a) measured in the WHEL study, b) self-reported in the NHS, and c) self-measured based on instructions provided by the study in LACE. BMI was grouped according to the following World Health Organization International Classifications [12]: underweight (<18.5 kg/m^2), normal weight (18.5–24.99 kg/m^2), overweight (25–29.99 kg/m^2), obese I (30–34.99 kg/m^2), and obese II ($\geq$35 kg/m^2).

Very low physical activity

Physical activity levels were ascertained by study-specific questionnaires and were converted into metabolic equivalent (MET) hours per week. Very low physical activity was defined as an extremely low level of physical activity consistent with a sedentary lifestyle (<1.5 MET h/wk) (equivalent to <30 min of moderate paced walking per week) [13]. The WHEL study used a standardized questionnaire to assess the frequency, duration, and speed of walking outside the home, as well as frequency and duration of participating in each of the three intensity levels of exercise (mild, moderate, and strenuous exercise). WHEL physical activity measures have been validated against a physical activity recall and accelerometry [14]. The NHS used a validated physical activity questionnaire to collect information on participation in a variety of commonly reported recreational activities. The NHS questionnaire has been validated against physical activity diaries [15]. Physical activity was assessed in the LACE Study with a questionnaire adapted from the Arizona activity frequency questionnaire. This questionnaire assesses recreational activity and has been validated against doubly labeled water [16].

This analysis focused on post-diagnosis physical activity which was determined based on activity data that were obtained between 18 and 48 months post-diagnosis and combined information on intensity [17] with frequency and duration of activity.

Comorbidities

Comorbidities were ascertained by self-report in all three cohorts. For this analysis, the presence of selected comorbidities was categorized as none, diabetes only, hypertension only, or a combined diagnosis of diabetes and hypertension. As WHEL was missing information on cardiovascular disease (CVD—i.e., myocardial infarction and stroke), for this analysis, we excluded participants with a diagnosis of only CVD from the other two cohorts ($n = 84$). Those with CVD plus another comorbidity (hypertension or diabetes) were classified based on the non-CVD comorbidity ($n = 270$).

Ascertainment of outcomes

Outcomes of interest include breast cancer-specific mortality and all-cause mortality. Overall survival was the time from cancer diagnosis to death from breast cancer or all-cause at the end of follow-up. Deaths were obtained through periodic reviews of the social security death index, national death index, and medical records, as well as family member reports and the postal service. Cause of death was determined from National Death Index records, death certificates, or medical records. Details regarding outcome ascertainment have been published [8].

Recurrence was not analyzed as an outcome because NHS did not assess breast cancer recurrences among breast cancer patients until the year 2000 (9 years after the 1991 initial diagnosis inclusion date for this analytical sample). In addition, after 2010, WHEL ascertained only breast cancer death, not recurrence. Participants were followed for an average of 11.8 years (SD = 3.98) after initial breast cancer diagnosis.

Statistical analyses

We used the Q statistic to test for heterogeneity in risk estimates across studies [8, 18]. This was not statistically significant ($p_{het} > 0.05$); thus, individual data from the three cohorts were combined. Differences in pooled mortality rates (breast cancer and all-cause) across categories for each of the three lifestyle variables were assessed using Chi-squared tests. A pooled survival analysis was conducted using delayed entry Cox proportional hazards models, stratified by cohort, with time (in years) since original diagnosis as the delayed entry parameter, in order to control for potential bias associated with participants entering the study at different times following diagnosis. All models were adjusted for race/ethnicity, age at diagnosis in years, TNM stage (I, II, III), histologic grade (well, moderately, poorly, and unspecified), ER status (ER+, ER−), history of chemotherapy, and pack-years of smoking.

The proportional hazards assumption was examined for all models by testing the significance of product terms for our variables of interest and log time, and by using the Wald test for proportional hazards. Delayed entry Cox proportional hazards models examined each lifestyle predictor (BMI, low physical activity, and comorbidities) sequentially and together in multivariate models for all-cause mortality. All tests were two-sided, and analyses were conducted in SAS version 9.4 (Cary, N.C).

Results

The mean [standard deviation (SD)] age at breast cancer diagnosis was 59.0 (10.5) years, 72.6 % of the women were post-menopausal at diagnosis, the sample was largely non-Hispanic white (88.6 %), and the average pack-year smoked was 22.1 (20.1) years among the 53 % that reported being current or former smokers. Overall, 51.4 % of study participants were diagnosed with Stage I cancer. Detailed information on the demographic and clinical characteristics of the individual and pooled cohort were published elsewhere [8]. The mean (SD) post-diagnosis BMI was 27.2 kg/m^2 (6.0), with 1.5 % underweight (BMI <18.5), 33 % overweight (BMI 25–29.9), 15.5 % obese I (BMI 30–34.9), and 9 % obese II (BMI ≥35). The mean (SD) post-diagnosis physical activity was 12.57(16.6) MET h/week; 24 % reported less than 1.5 MET h/week. Overall, 63.5 % of participants had no comorbidities, 2 % had diabetes only, 30 % had hypertension only, and 4.5 % had a combined diagnosis of diabetes and hypertension. Over a mean (SD) follow-up of 11.8 (3.98) years, there were 1131 breast cancer-specific deaths and 2212 deaths due to all causes. The mean (SD) time from diagnosis to death was 7.8 (4.1) years for breast cancer-specific death and 8.8 (4.3) years for all-cause mortality (Supplemental Table A.).

Table 1 gives the percent mortality (breast cancer specific and overall) within each BMI, comorbidity, and physical activity category as well as the p value for differences in mortality across category. Breast cancer-specific mortality was highest in underweight women (15.1 %), but lower and relatively constant in the other 4 BMI categories; this difference was not statistically significant ($p = 0.155$). All-cause mortality was also highest in underweight women (48.2 %), but again lower and relatively constant in the other 4 BMI categories, ($p < 0.0001$). Breast cancer mortality was highest in those with diabetes (14.8 %), although it was only marginally significant ($p = 0.055$). All-cause mortality was different between comorbidity groups ($p < 0.0001$) and was much

Table 1 Breast cancer-specific (BCA) and all-cause mortality by risk factor category in a pooled cohort of US breast cancer survivors

	% Mortality during follow-up		
		Pooled	
		BCA	All-cause
Overall	Deaths/N	1131/9513	2212/9513
	Overall mortality	11.90 %	23.30 %
Body mass index	Underweight (<18.5)	15.10 %	48.20 %
	Normal (18.5–24.9)	11.00 %	21.00 %
	Overweight (25.0–29.9)	12.30 %	23.20 %
	Obese I (30.0–34.9)	13.10 %	25.60 %
	Obese II (≥35.0)	11.60 %	25.60 %
	p value[a]	0.155	<0.0001
Comorbidities	None	11.80 %	19.00 %
	Diabetes	14.80 %	35.70 %
	Hypertension	11.60 %	28.20 %
	Hypertension & diabetes	13.00 %	44.70 %
	p value[a]	0.545	<0.0001
Physical activity	Low (MET h/week <1.5)	14.70 %	31.80 %
	Not-low (MET h/week ≥1.5)	11.20 %	21.20 %
	p value[a]	<0.0001	0.0001

[a] Chi-squared test

higher in those with both diabetes and hypertension (44.7 %) than in those with neither comorbidity.

Lastly, both breast cancer-specific and all-cause mortality were highest among women with very low physical activity (14.7 and 31.8 %), ($p < 0.0001$) for each.

Table 2 presents the delayed entry Cox proportional hazards models of the association of BMI, very low physical activity, and comorbidities, with breast cancer-specific mortality. In multivariate models without the other two target variables, models 1–3, very low physical activity, model 3, was significantly associated with a 22 % increased risk of breast cancer mortality (HR 1.22, 95 % CI 1.05, 1.42). In the major comorbidities model, model 2, the closest to statistical significance was a diagnosis of diabetes (HR 1.49, 95 % CI 0.99, 2.23, $p = 0.055$). In the BMI model, model 1, there was no significant association with risk of breast cancer mortality. These results were essentially unchanged with all variables in a joint model, model 4.

The models for all-cause mortality are presented in Table 3 which shows the delayed entry Cox proportional hazards models of the association of BMI, very low physical activity, and select comorbidities. For all-cause mortality, the physical activity model, model 3, showed a significant 43 % increase in risk associated with very low physical activity (HR 1.43, 95 % CI 1.29, 1.59). In the comorbidity model, model 2, diabetes and hypertension significantly increased the risk of all-cause mortality by 89 and 30 %, respectively. Having both conditions was associated with a significant, 2.3-fold increase in all-cause mortality (HR 2.29, 95 % CI 1.91, 2.74). In the BMI model, model 1, being underweight was associated with a significant 2.5-fold increase in risk of all-cause mortality, and there was a 20 and 30 % increase in risk associated with being obese (Obese I HR 1.19, 95 % CI 1.05, 1.36, Obese II HR 1.31, 95 % CI 1.12, 1.54). When all three risk factors were modeled together, model 4, the risk associated with being obese was completely attenuated and became non-significant (Obese I HR 1.06, Obese II HR 1.05), and only underweight remained significant, while the significance, strength, and direction of the association of comorbidities and physical activity with all-cause mortality remained constant.

Discussion

The results of this analysis indicate that in this large cohort of US breast cancer survivors, very low physical activity, consistent with a sedentary lifestyle, is a significant risk factor for breast cancer mortality. There was no association between post-diagnosis obesity and breast cancer mortality. Further, the association between post-diagnosis obesity and all-cause mortality was completely attenuated after adjustment for very low physical activity and select comorbidities. To date, relatively few studies have investigated post-diagnosis (≥12 months) BMI and mortality in breast cancer survivors [19]. Those that have investigated

Table 2 Cox proportional hazards model for lifestyle/comorbidity variables and breast cancer-specific mortality in a pooled cohort of US breast cancer survivors ($n = 9513$)

	Deaths/N	Model 1	Model 2	Model 3	Model 4
Body mass index					
Underweight (<18.5)	21/139	1.45 (0.83–2.53)			1.41 (0.81–2.45)
Normal (18.5–24.9)	429/3889	Reference			Reference
Overweight (25.0–29.9)	389/3154	1.07 (0.92–1.25)			1.05 (0.90–1.22)
Obese I (30.0–34.9)	192/1471	1.10 (0.91–1.33)			1.04 (0.86–1.27)
Obese II (≥35.0)	100/860	1.05 (0.83–1.32)			0.95 (0.74–1.20)
Comorbidities					
None	715/6037		Reference		Reference
Diabetes	29/198		1.49 (0.99–2.23)*		1.43 (0.95–2.15)*
Hypertension	332/2855		1.12 (0.96–1.31)		1.11 (0.95–1.30)
Hypertension & diabetes	55/423		1.34 (0.97–1.85)*		1.32 (0.95–1.84)*
Physical activity					
Low (MET h/week <1.5)	274/1865			1.22 (1.05–1.42)**	1.21 (1.03–1.41)**
Not-low (MET h/week ≥1.5)	857/7648			Reference	Reference

All models controlled for race/ethnicity, stage, grade, age diagnosed, estrogen receptor status, chemotherapy, pack-years smoked, and current smoking

Model 1 BMI on breast cancer-specific mortality; *Model 2* comorbidities on breast cancer-specific mortality; *Model 3* physical activity on breast cancer-specific mortality; *Model 4* BMI, comorbidities, and physical activity on breast cancer-specific mortality

* p value < 0.1, ** p value < 0.05

Table 3 Cox proportional hazards model for lifestyle/comorbidity variables and all-cause mortality in a pooled cohort of US breast cancer survivors ($n = 9513$)

	Deaths/N		Model 1	Model 2	Model 3	Model 4
Body mass index						
Underweight (<18.5)	67/	139	2.48 (1.84–3.34)**			2.32 (1.72–3.12)**
Normal (18.5–24.9)	817/	3889	Reference			Reference
Overweight (25.0–29.9)	731/	3154	1.05 (0.94–1.17)			1.00 (0.89–1.11)
Obese I (30.0–34.9)	377/	1471	1.19 (1.05–1.36)**			1.06 (0.92–1.21)
Obese II (≥35.0)	220/	860	1.31 (1.12–1.54)**			1.05 (0.88–1.24)
Comorbidities						
None	1148/	6037		Reference		Reference
Diabetes	70/	198		1.89 (1.45–2.45)**		1.77 (1.36–2.30)**
Hypertension	805/	2855		1.30 (1.17–1.44)**		1.27 (1.14–1.42)**
Hypertension & diabetes	189/	423		2.29 (1.91–2.74)**		2.16 (1.79–2.60)**
Physical activity						
Low (MET h/week <1.5)	594/	1865			1.43 (1.29–1.59)**	1.35 (1.22–1.51)**
Not-low (MET h/week ≥1.5)	1618/	7648			Reference	Reference

All models controlled for race/ethnicity, stage, grade, age diagnosed, estrogen receptor status, chemotherapy, pack-years smoked, and current smoking

Model 1 BMI on all-cause mortality; *Model 2* comorbidities on all-cause mortality, *Model 3* physical activity on all-cause mortality; *Model 4* BMI, comorbidities, and physical activity on all-cause mortality

** p value < 0.05

this focused primarily on change in BMI following diagnosis [20–24] rather than purely on post-diagnosis BMI [25]. For prevention of long-term outcomes, it is the BMI post-diagnosis that should be the most focal to examination. Our results strengthen the conclusion that there is no relationship between post-diagnosis obesity and death [25]. Our findings are also consistent with research showing that, in the general population, physical activity attenuates the mortality risks associated with obesity [26], that PA is associated with a reduced mortality risk in post-menopausal women [27], and that PA is associated with decreased mortality in breast cancer survivors [28].

Recently, there has been interest in whether the physical activity effect might relate more to sedentary behavior (i.e., most of the day sitting or reclining). Our cohorts did not query sedentary behavior so we are unable to address this issue. However, most women in this study who achieved less than 1.5 MET hours per week might be expected to be classified as sedentary if the appropriate questions were included in this study. Thus, our study reports on very low physical activity which may be consistent with sedentary lifestyle. A limitation with our study is that our measure of physical activity emphasized self-report which has been shown to be associated with considerable error [29, 30] although each cohort used a validated questionnaire. Finally, since BMI, the presence of comorbidities, and physical activity were all assessed at the same approximate time point, we are unable to assess the temporality of these three lifestyle risk factors. Further study is needed to allow a mediation analyses between these risk factors.

The most prominent strength of this analysis is the large sample size. In addition, the pooling of several cohorts allows us to consistently control for important confounding factors and avoid the heterogeneity between studies that can confuse the findings of meta-analyses, while maximizing variability in the exposures of interest, allowing a more thorough investigation of these factors than in any one cohort analyzed individually.

In conclusion, these findings suggest that very low physical activity post-diagnosis is an important risk factor for breast cancer-specific mortality. For all-cause mortality, the major risk factors were very low physical activity and selected comorbidities. Further studies are needed to elucidate whether this very low physical activity effect comes from sedentary behavior. Although needing further validation, these findings suggest that treatment for comorbidities, and especially interventions to increase activity in those with a sedentary lifestyle, should become a priority for breast cancer survivors.

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Conflict of interest The authors declare that they have no conflict 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 committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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