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Report

Obesity and cardiovascular risk factors in younger breast cancer survivors: The Cancer and Menopause Study (CAMS)

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Summary

Background. Breast cancer patients today can expect long-term survival; however, weight gain is a common problem after treatment and increases the risk for recurrence, cardiovascular disease and diabetes. The multi-ethnic cohort from the Cancer and Menopause Study, designed to examine the reproductive and late cardiovascular health effects of treatment in younger female breast cancer survivors (BCS), was used to describe the relationship of behavioral and treatment variables to body mass index (BMI), physical activity (PA), and cardiovascular risk factors.

Methods. Stage 0, I or II breast cancer survivors who were ≤ 50 years at diagnosis and 2–10 years disease-free survivors (mean 5.9 ± 2.3 years) were recruited from two tumor registries to complete a mail survey that included information on demographics, health-related quality of life, reproductive health, cancer treatment, PA, weight and height. A sub-sample completed an office visit where fasting blood lipids, blood pressure (BP), height and weight were measured. Linear regression analysis was used to model the following outcomes: BMI, PA, blood lipids and BP.

Results. Current BMI was positively associated with higher BMI prior to diagnosis, unhappiness with body image and negatively associated with current total PA (model $p < 0.001$). More work, home and leisure PA were all positively associated with greater physical functioning and higher energy levels (all models, $p < 0.001$). Total and LDL cholesterol were positively associated with number of years since diagnosis and negatively associated with leisure PA (both models, $p < 0.001$), while systolic and diastolic BP were both positively associated with age, current use of BP medications and current BMI (models, $p < 0.001$).

Conclusions. Obesity in these BCS is prevalent and associated with premorbid obesity and decreased current physical activity but not with adjuvant treatment. Given the negative health consequences of weight gain and obesity after breast cancer, continued study of the etiology of weight gain, and potential targets for weight gain prevention are required. Interventions that target PA may be important for weight maintenance in BCS.

Introduction

Women are surviving breast cancer at increasing rates [1,2] with current 5-year survival rates of 88% [3]. There are more than two million breast cancer survivors in the US alone [4–6]. Many breast cancer survivors experience side effects secondary to treatment that affect their ongoing health both physically and mentally [7–10]; these adverse effects may be especially problematic for younger women [11]. Treatment with chemotherapy in younger women may lead to early menopause [12] with consequent weight gain [13–15]. Weight gain may potentially put breast cancer survivors at increased risk for future recurrence of cancer, cardiovascular disease and diabetes [13,16,17]. Moreover, obesity in breast cancer patients is a significant unfavorable prognostic factor for survival [18–22]. Dignam and colleagues [23] recently examined the relationship between obesity and breast cancer recurrence in women with early-stage, estrogen-receptor positive breast cancer enrolled in National Surgical Adjuvant Breast and Bowel Project (NSABP) treatment trials. They found that the risk of breast cancer recurrence was the same among obese women as underweight or normal weight women. However, obese women had a higher risk for contralateral breast cancer, and other primary cancers in addition to greater all-cause mortality than normal-weight women.

Obesity also predisposes women to higher risks for cardiovascular disease [24,25]. Among these are higher blood pressure and an unfavorable lipid profile. In a study of competing risks for mortality among breast cancer patients, the authors found that the probability of death from other causes generally increased with increasing age, and that for early stage breast cancer patients, non-cancer causes of death predominate [26]. Little is known about whether or not the premature occurrence of menopause induced as part of treatment in younger breast cancer patients increases the frequency or severity of subsequent adverse cardiovascular risk factors. As more women continue to survive breast cancer, there is increasing concern about competing causes of morbidity and mortality [26], and a greater emphasis will need to be placed on strategies to modify these competing health risks.

The Cancer and Menopause Study (CAMS) was initiated in 1997 to examine the reproductive and late health outcomes in younger breast cancer survivors who had been diagnosed at ≤ 50 years of age and were recruited into the cohort study between 2–10 years later [11,27]. We have previously described the medical, demographic, reproductive, and quality of life outcomes from the cohort of 577 survivors [11], as well as menopausal symptoms [28] and bone density findings [29]. In this paper we examine the frequency of obesity and cardiovascular risk factors in this cohort, and explore the variables that may contribute to obesity after breast cancer treatment including demographic, treatment, reproductive, symptoms, physical activity and quality of life. We believe that this hypothesis-generating study is one of the first to consider long-term obesity and cardiovascular risk factors in this patient population.

Materials and methods

Study cohort

The CAMS cohort included 577 women, who were 50 years of age or younger and diagnosed between 1987 and 1997 [27]. Subjects were identified from tumor registry listings from two Los Angeles hospitals. The recruitment procedures and the study design have been described in detail elsewhere [11,27], but will be outlined briefly here. Study eligibility included: (1) diagnosis with first invasive or non-invasive breast cancer (ductal carcinoma *in situ*);(2) being alive and disease-free; (3) no other malignancies prior to the breast cancer diagnosis; and (4) stage 0, I, or II disease according to the tumor registry records. Potentially eligible women were invited by mail to participate in the study ($n = 1440$). Mailed responses from 71.5% ($n = 1029$) were received. These respondents were screened by telephone interview to confirm eligibility and were then mailed an informed consent form and the study questionnaire ($n = 736$). Five hundred and seventy seven women satisfactorily completed baseline questionnaires (78% of women who were mailed questionnaires). Multiple attempts were made to contact the non-respondents ($n = 411$). Reasons for non-response included: inability to contact by telephone or mail (84%), deceased (7%), and ineligible because they could not read or understand English (9%). A sub-sample of the CAMS cohort was invited back approximately 6 months following the original mailed survey for an in-person office visit to measure height, weight, blood pressure, lipid panel, and bone density. Eligibility for the in-person visit was being geographically accessible and willing to come in for an in-person visit. The analytical sample for this study was made up of 343 women (59% of the CAMS sample that returned mailed questionnaires) (see Figure1). For the remainder of this manuscript, the main survey cohort will be referred to as the mail-only sample and the women who came for the in-person office visit will be referred to as the in-person visit sub-sample. The study was approved by the UCLA Institutional Review Board and written consent was obtained from each participant [27].

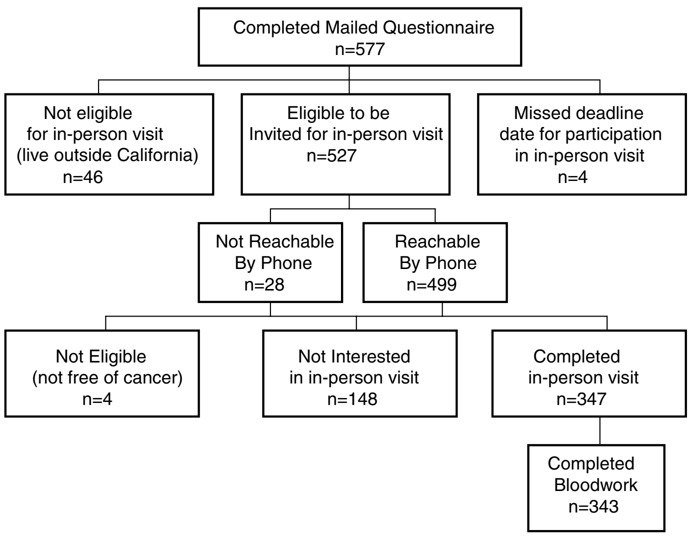

Figure 1. Recruitment Flow Chart for In-person Visit Sub-sample.

Survey instruments

The content of the full study survey is described elsewhere [11]. This report includes data from the following sections of the survey: demographic information, breast cancer treatment information, health-related problems, menopausal status, quality of life (QOL), tobacco and alcohol use, physical activity (PA), anthropometrics, and biological endpoints. These variables were chosen for analysis due to their demonstrated association with the outcomes of interest in the literature. Demographic and breast cancer treatment information (e.g., type of surgery, chemotherapy, radiation and tamoxifen) were obtained using questions from a series of prior studies [8,30, 31]. Questions pertaining to past health and medical history were obtained through self-report in response to a list of nineteen conditions with response choices including "no, never," "yes, in past (more than 1 year ago)", and "yes, now (during the past year)."

Current symptoms were assessed using The Breast Cancer Prevention Trial Symptom Checklist [32,33], which includes a list of 42 everyday problems. Respondents rated how much they were bothered by each symptom during the past 4 weeks on a 5-point Likert-type scale from "0 = not at all" to "4 = extremely."

Definitions of menopausal status were menstrually based. Descriptions of how women were assigned to a particular stage of menopause (pre-, peri-, post-) are described in Ganz et al. [11]. Briefly, women were defined as *pre-menopausal* if they had regular menstrual periods, *peri-menopausal* if their periods were irregular compared to their own baseline or if they had had a gap of at least 3 months but not more than 6 months in their menstrual periods, and *post-menopausal* at survey if they had experienced cessation of menstrual periods for at least 6 months after breast cancer treatment or at least 12 months before cancer diagnosis. At the time of the in-person visit, menstrual status was re-assessed by asking women if they were currently menstruating (classified as pre-/peri-menopausal) or not (classified as postmenopausal).

Health-related QOL was assessed with the RAND SF-36 (also known as the MOS-SF-36) [34,35]. The RAND SF-36 contains eight individual scales: physical functioning; role function, physical; bodily pain; social functioning; mental health; role function, emotional; vitality (energy and fatigue); and general health perceptions [34,35]. Each scale is scored from 0 to 100, with 100 being the most favorable score. Depressive symptoms were assessed using the Center for Epidemiologic Studies-Depression Scale (CES-D), a 20-item self-report scale developed for the general population [36]. Higher scores on the CES-D indicate greater risk of depression, with scores of 16 or greater indicating an increased risk of clinical depression [36].

Participants reported their tobacco and alcohol use in response to the following questions: "Have you smoked at least 100 cigarettes in your entire life?" and "In the last 12 months have you had at least 12 drinks of any kind of alcoholic beverage?" Response categories were either "yes" or "no".

Outcome measures used in analyses included BMI, PA, blood lipids and blood pressure. Participants reported their height and weight at time of the breast cancer diagnosis and at time of the mailed questionnaire. BMI was calculated as weight divided by height squared (kg/m^2). Reliability of these self-report data from the mailed survey was examined in the in-person sample where height and weight were measured.

PA was measured using the Post-menopausal Estrogens and Progestins Intervention (PEPI) PA assessment questionnaire (PEPI-Q). The construct validity of the PEPI-Q was established in the PEPI study [37] and in the Women's Ischemia Syndrome Evaluation Study (WISE) cohort where it was statistically significantly associated with fitness directly measured as exercise capacity by treadmill testing [38,39]. We used the PEPI-Q to evaluate three domains of usual PA in the year prior to the mailed survey: work, home and leisure [38]. For each domain, women were asked to respond to the question, "How would you describe the kind of physical activity you performed?" Response categories included 1 = inactive, 2 = light, 3 = moderate, and 4 = heavy.

For women who participated in the in-person sample, a research assistant collected blood, measured blood pressure, weight, height, and waist and hip circumference. Weight and height were measured on a balance beam scale in light clothing with a stadiometer to measure height. Waist circumference was measured at the umbilicus and hip circumference at the maximal circumference over the buttocks. Waist-to-hip circumference was calculated as 100 × maximal waist circumference in cm/maximal hip circumference in centimeters. All subjects had fasted for 12 h prior to the appointment at which time blood was drawn for the cardiovascular lipid panel. The lipid panel included total cholesterol, low-density lipoproteins (LDL) and high-density lipoproteins (HDL), and was measured in the clinical laboratory at the UCLA Medical Center.

Data analysis

Statistical analyses were conducted using SPSS version 10.1 [40]. Outcome variables were described with means and standard deviations. One-way analysis of variance (ANOVA) was used to compare outcome variables – BMI (continuous), PA (ordinal), cholesterol levels (continuous), and blood pressure (continuous) – across categories of demographic, treatment, health-related problems, menopausal, QOL, tobacco and alcohol use variables. χ^2 tests (categorical variables) and Pearson correlations (continuous variables) were utilized to test for statistically significant bivariate associations between outcome and predictor variables. Linear regression was used to model the BMI and PA outcomes at the time of the mailed questionnaire. Regression was also used to model the components of the lipid profile and blood pressure (systolic and diastolic) outcomes at the time of the in-person visit sub-study.

Results

Characteristics of the study samples

Table 1 shows demographic characteristics, menopausal status, and type of adjuvant therapy of participants in the mail-only sample compared to those in the in-person sample. Although 577 women completed the mailed survey [27], the analytical sample was smaller ($n=441$) due to missing data for some variables: 56 women who had unclassifiable menopausal status, 56 who did not report any work PA, 15 with missing data on tamoxifen use, and 9 who did not report their income. Some data were also missing from the 343 women in the in-person visit sample including 28 who did not report any work PA, 11 with unclassifiable menopausal status, 9 with missing lipid values, and 6 who did not report their income. Table 2 shows a comparison BMI, PA and life-

Table 1. Demographic characteristics, menopausal status, and type of adjuvant therapy for the CAMS Cohort

	Mail-only Sample ($n=441$) mean ± sd (min−max)	In-person visit sub-sample[a] ($n=289$) mean ± sd (min−max)
Current age	49.2 ± 5.9 (30.0−61.6)	49.8 ± 5.6 (32.3−61.4)
Age at diagnosis	43.4 ± 5.4 (25.2−51.0)	43.5 ± 5.2 (27.6−51.0)
Years since diagnosis	5.8 ± 2.3 (1.5−11.4)	6.3 ± 2.5 (2.1−12.7)
	N (%)	N (%)
Education		
Highschool or less	24 (5.4)	14 (4.8)
Vocational training	21 (4.8)	13 (4.5)
Some college	121 (27.4)	91 (31.5)
College graduate	84 (19.0)	53 (18.3)
Postgraduate education	191 (43.3)	118 (40.8)
Employment status		
Working full or part-time	376 (85.3)	243 (84.1)
Not working	65 (14.7)	46 (15.9)
Ethnicity		
White	305 (69.2)	198 (68.5)
Black	49 (11.1)	34 (11.8)
Hispanic	34 (7.7)	24 (8.3)
Asian	43 (9.7)	25 (8.6)
Other	10 (2.3)	8 (2.8)
Income		
< $15,000	5 (1.1)	1 (0.3)
15,000–30,000	28 (6.3)	17 (5.9)
30,001–45,000	55 (12.5)	36 (12.5)
45,001–60,000	41 (9.3)	30 (10.4)
60,001–100,000	154 (34.9)	101 (34.9)
>100,000	158 (35.8)	104 (36.0)
Partner status		
Partnered	306 (69.4)	203 (70.2)
Not partnered	135 (30.6)	86 (29.8)
Menopausal status[b]		
Premenopausal	79 (17.9)	73 (25.3)
Perimenopausal	65 (14.7)	–
Postmenopausal	297 (67.3)	216 (74.7)
Type of adjuvant therapy		
No treatment	110 (24.9)	71 (24.6)
Tamoxifen only	40 (9.1)	38 (13.1)
Chemotherapy only	171 (38.8)	103 (35.6)
Tamoxifen and Chemotherapy	120 (27.2)	77 (26.6)

[a]All variables except demographics and type of treatment were re-assessed at the time of the in-person visit sub-sample, which was conducted with a subsample of the mail-only cohort approximately 6 months after the mailed survey was administered.
[b]Menopausal status for the in-person visit sub-sample was determined in response to the question: Are you currently menstruating? (yes/no). Those who reported currently menstruating were classified as pre-menopausal.

Table 2. Body mass index, physical activity, and lifestyle variables for the CAMS Cohort

	Mail-only sample ($n=441$) mean ± sd (min−max)	N (%)	In-person visit sub-sample[a] ($n=289$) mean ± sd (min−max)	N (%)
BMI	25.3 ± 5.4 (16.5−53.4)	–	25.6 ± 5.4 (17.3−43.0)	–
< 25 kg/m^2	–	250 (56.9)	–	157 (55.1)
25–30 kg/m^2		118 (26.9)		69 (24.2)
> 30 kg/m^2		71 (16.2)		59 (20.7)
Total physical activity[b]	7.08 ± 2.0 (3−12)	–	7.06 ± 2.0 (3−12)	–
Work PA	2.21 ± 0.84 (1−4)	–	2.22 ± 0.85 (1−4)	–
Inactive	–	92 (20.9)	–	59 (20.4)
Light		194 (44.0)		128 (44.3)
Moderate		126 (28.6)		82 (28.4)
Heavy		29 (6.6)		20 (6.9)
Home PA	2.34 ± 0.74 (1−4)	–	2.33 ± 0.78 (1−4)	–
Inactive	–	48 (10.9)	–	35 (12.1)
Light		218 (49.4)		144 (49.8)
Moderate		151 (34.2)		90 (31.1)
Heavy		24 (5.4)		20 (6.9)
Leisure PA	2.53 ± 0.81 (1−4)	–	2.52 ± 0.81 (1−4)	–
Inactive	–	43 (9.8)	–	27 (9.3)
Light		165 (37.6)		116 (40.1)
Moderate		186 (42.4)		115 (39.8)
Heavy		45 (10.2)		31 (10.7)
Ever smoker				
Yes	–	181 (41.0)	–	119 (41.2)
Alcohol intake[c]				
Yes	–	247 (56.0)	–	163 (56.4)
Variables measured at the in-person visit only[d]				
Total cholesterol (mm/dL)			204.5 ± 37.3 (74.0−355.0)	
<200	–	–		136 (47.1)
200–239				103 (35.6)
≥240				50 (17.3)
LDL cholesterol (mm/dL)			124.4 ± 33.5 (38.0−239.0)	
<100				64 (22.1)
100–129				109 (37.7)
130–159				73 (25.3)
160–189				33 (11.4)
≥190				9 (3.1)
HDL cholesterol (mm/dL)			64.0 ± 16.8 (24.0−142.0)	
<40				8 (2.8)
40–59				113 (39.1)
≥60				168 (58.1)
Systolic BP (mm Hg)				
<140	–	–	121.3 ± 15.8 (94.0−190.0)	246 (85.1)
≥140				41 (14.2)
Diastolic BP (mm Hg)			81.4 ± 10.2 (58.0−118.0)	
<90				218 (75.4)
≥90				69 (23.9)
Waist circumference (cm)			80.8 ± 13.1 (57.2−119.4)	
Hip circumference (cm)			104.1 ± 12.4 (66.1−171.8)	
Waist-to-hip ratio			0.77 ± 0.08 (0.49−1.34)	
<0.8				192 (66.4)
≥0.8				94 (32.5)

[a]All variables were collected by self-report at the time of the mailed questionnaire. BMI was also measured at an in-person interview, which was conducted with a subsample of the mail-only cohort approximately 6 months after the mailed questionnaire was administered.
[b]The categories for physical activity were scored as follows: inactive = 1; light = 2; moderate = 3; heavy = 4.
[c]Participants responded to the question: ''In the last 12 months have you had 12 drinks of any kind of alcoholic beverage?'' (yes/no).
[d]The National Cholesterol Education Program (NCEP) criteria were used to evaluate cholesterol and blood pressure values [62].

style variables of the mail-only sample and the in-person sub-sample. The samples for this analysis are similar with respect to all of the variables shown in Tables 1 and 2. These survivors were about 49 years of age on average at the time of the mailed questionnaire and were about 5.8 years since diagnosis of breast cancer. They were largely well-educated, working, and were also ethnically diverse (31% non-White). Two-thirds were postmenopausal at the time of survey and only one-quarter had not received any form of adjuvant therapy.

To assess the reliability of self-reported height and weight obtained from the mail-only sample, we compared those values with height and weight measured in the in-person visit sub-sample for women who had both values. The correlation between self-reported and measured height was $r = 0.952$ ($p < 0.001$) and for weight was $r = 0.978$ ($p < 0.001$). A smaller proportion of women in the mail-only sample were classified as obese (BMI > 30 kg/m^2) when compared to those in the in-person sub-sample (16.2% versus 20.7%). Proportions of obesity are lower than the figure of 33% reported for the general population of U.S. women in this age group [41].

Approximately 35% of women reported engaging in moderate to heavy work activity, 39% in moderate to heavy home activity and over 50% reported moderate to heavy leisure time physical activity. Comparison of the mail-only sample and the in-person sub-sample showed only minor differences in levels of PA. Slightly over 40% of the women reported ever smoking, although only 4.1% were current smokers (data not shown), and about 56% reported some intake of alcoholic beverages.

For the variables available only for the in-person sub-sample, we found that women on average had total cholesterol levels that were "borderline high", mean LDL cholesterol levels that were "near optimal" and mean HDL cholesterol levels that were considered "high" according to NCEP criteria [42]. Women's mean systolic and diastolic blood pressures were both in the "desirable" range. The average waist circumference was in the normal range as was the waist-to-hip ratio [43,44]. The current guidelines recommend that a single waist circumference threshold (men: 102 cm; women: 88 cm) be used to denote a high waist circumference, regardless of BMI category [44]. These gender-specific thresholds were originally developed in a large sample of white men and women in which a waist circumference of 102 cm in men and 88 cm in women corresponded to a BMI of 30.0 kg/m^2.

Characteristics associated with obesity in breast cancer survivors

Although obesity could be quantified by several different outcome measures (e.g., weight, BMI, or waist/hip circumference), for our analyses we have used BMI categories as our measure of obesity. We then selected variables from the mailed questionnaire known to be associated with obesity [13,14] as well as breast cancer treatment variables, for initial exploration of factors associated with BMI. These variables included demographic factors (age at time of survey, ethnicity, years of education completed, income, and marital status), treatment variables (years since diagnosis, comorbidities in the year before the survey, treatment with chemotherapy, and current use of tamoxifen), menopausal status (at time of the mailed questionnaire) health-related symptoms (BCPT symptoms, global health perception), and QOL (the SF-36 scales and CES-D). The decision to retain predictor variables in the modeling process was based on a statistically significant association (Pearson's product moment correlation, ANOVA test or χ^2, $p < 0.05$) with BMI.

Multiple linear regression modeling (mean of 5.3 years after diagnosis at time of the mailed questionnaire) revealed a significant positive association between BMI at the time of cancer diagnosis ($p < 0.0001$), non-white ethnicity ($p = 0.009$), income less than \$75,000 ($p = 0.03$), longer time since diagnosis ($p < 0.0001$), currently engaging in less total PA ($p = 0.02$) and being unhappy with body image ($p < 0.0001$) (see Table 3). The adjusted R^2 for this model was 0.75 and was statistically significant ($p < 0.0001$). Interestingly, treatment variables (chemotherapy, tamoxifen) and menopausal status were not significantly associated with obesity in this long-term survivor sample.

Characteristics associated with physical activity in breast cancer survivors

Because higher total PA was statistically significantly associated with BMI, and because PA is a modifiable factor, we next explored the domain specific PA. We conducted regression analyses with each of the three domains of PA: work, home and leisure as outcomes. As with BMI, we chose as candidate predictors those that had been demonstrated in the literature to be associated with PA including demographic factors (age at time of survey, ethnicity, years of education completed, income, and marital status), treatment variables (years since diagnosis, comorbidities in the year before the survey, treatment with chemotherapy, and current use of tamoxifen), menopausal status (at time of the mailed questionnaire), health-related symptoms (BCPT symptoms, global health perception), QOL (the SF-36 scales and CES-D), and lifestyle variables (tobacco and alcohol use). Bivariate analyses were conducted for all three domains of PA with each of the variables in these groups. Variables were entered in the modeling procedure based on a statistically significant bivariate test. We found that women engaged in more *work activity* if they were younger ($p = 0.04$), reported income less than \$75,000 ($p = 0.02$), had more energy ($p = 0.002$), and better physical functioning ($p = 0.002$) (see Table 4). Greater home PA was associated with being married ($p = 0.001$), being either peri- or post-menopausal ($p = 0.04$), reporting more energy ($p = 0.008$) and having better physical functioning ($p = 0.02$). Greater leisure time PA was significantly associated with having at least a college education ($p = 0.009$), having a higher income

Table 3. Factors associated with BMI at time of the mailed survey ($n = 436$)

	BMI (kg/m^2)		
Model adjusted R^2(p-value)[a]	0.75 (< 0.0001)		
Parameter estimates	Coeff.(β)	Std. error	p^c
BMI at cancer diagnosis	**0.83**	**0.03**	**< 0.0001**
Age at survey	−0.009	0.03	0.75
Ethnicity-White	**−0.82**	**0.31**	**0.009**
College education	−0.002	0.45	0.96
Married/ Partnered	0.43	0.31	0.17
Income ≥75 K	**−0.65**	**0.30**	**0.03**
Time since diagnosis (years)	**0.37**	**0.07**	**< 0.0001**
Number of medical conditions	−0.18	0.14	0.22
Chemotherapy ever	0.15	0.30	0.62
Current tamoxifen use	0.09	0.37	0.81
Menopausal status at survey	0.27	0.41	0.51
Alcohol intake	−0.03	0.28	0.92
Total physical activity at time of the mailed questionnaire	**−0.17**	**0.07**	**0.02**
Unhappy w/body appearance	**1.20**	**0.13**	**< 0.0001**

[a]The following parameters were measured: dependent variables, BMI before cancer diagnosis, age at time of the mailed questionnaire, ethnicity (comparison group all other ethnicities), education (comparison group: high school education or less), married/partnered (comparison group: unpartnered), income (comparison group: income <$75,000), years since diagnosis, number of medical conditions, chemotherapy ever (comparison group: did not receive chemotherapy), current tamoxifen use (comparison group: not currently using), menopausal status at time of the mailed questionnaire (pre-menopausal versus peri-and post-menopausal), alcohol consumption during the past 12 months (comparison group: <12 alcoholic drinks), total PA at time of the mailed questionnaire (domains include work, home and leisure PA), unhappy with body appearance. Figures in bold indicate statistically significant parameters in each model.
[b]p-value from F-test for significant overall regression.
[c]p-value from t-tests of individual parameter estimates.

($p = 0.02$) and having more energy ($p = 0.003$) and better physical functioning ($p = 0.0002$). These models explained 9% of the variance for work activity, 11% for home activity, and 18% of leisure activity respectively (all $p < 0.0001$).

Characteristics associated with cardiovascular lipids and blood pressure

To better understand the association of obesity to cardiovascular risk in the in-person sub-sample, we calculated the proportion of women with high total cholesterol (>240 mg/dl) and hypertension (systolic BP ≥140 mm Hg and diastolic BP ≥90 mm Hg) by category of BMI and compared these data to a reference sample (data not shown). Women classified as overweight (BMI: 25–29.9 kg/m^2) in the in-person sub-sample had a lower prevalence of high cholesterol (44.5% versus 60.1%) and hypertension (23.8% versus 60.4%) than a similar aged sample of women from the 1999–2000 National Health and Nutrition Examination Survey (NHANES) population [45]. For women classified as obese (BMI:≥30 kg/m^2) the prevalence of high cholesterol and hypertension were also lower than the reference population but were within a much closer range (high total cholesterol: 24.2% versus 27.0% and hypertension: 31.8% versus 37.8% for the in-person sub-sample and NHANES samples respectively).

Using data from the in-person sub-sample, we examined the factors associated with women's blood lipids (Table 5). In preliminary bivariate analyses, we examined the relationship of the three domains of PA with blood lipids. Because only leisure PA was significantly associated, it was entered into our models. Other variables included in the regression models were demographics (age at the time of the in-person visit, ethnicity, years of education completed, income and marital status), treatment variables (years since diagnosis, treatment with chemotherapy, current use of tamoxifen, current use of cholesterol medication, and current use of blood pressure medication), menopausal status (menstruating at time of the in-person visit), BMI (measured at time of the in-person visit), and lifestyle variables (tobacco and alcohol use). Higher total cholesterol was significantly associated with a longer time since diagnosis ($p = 0.03$), and less leisure PA ($p = 0.004$). Demographics, treatment variables and menopause status were not significantly related to total cholesterol, nor was current BMI. The regression model for LDL cholesterol was similar to that for total cholesterol, however, BMI was also significant in this model ($p = 0.002$). For HDL cholesterol, higher level of education ($p = 0.05$), alcohol consumption ($p = 0.01$) and lower BMI ($p < 0.0001$) were all significantly associated with higher levels of HDL. These models explained 9% of the variance for total cholesterol, 14% for LDL cholesterol,

Table 4. Factors associated with work, home and leisure physical activity at time of the mailed questionnaire[a]

	Dependent variable								
	Work activity ($n=440$)			Home activity ($n=440$)			Leisure activity ($n=439$)		
Model adjusted R^2 (*p*-value)[b]	0.09 (< 0.0001)			0.11 (< 0.0001)			0.18 (< 0.0001)		
Parameter estimates	Coeff. (β)	Std. error	p^c	Coeff. (β)	Std. error	p^c	Coeff. (β)	Std. error	p^c
Age[a]	**−0.02**	**0.01**	**0.04**	−0.009	0.01	0.24	−0.01	0.01	0.18
Ethnicity-White	−0.02	0.09	0.85	0.001	0.08	0.99	0.06	0.08	0.44
College education	0.26	0.13	0.05	0.04	0.11	0.74	**0.31**	**0.12**	**0.009**
Married Partnered	0.10	0.09	0.26	**0.26**	**0.08**	**0.001**	0.02	0.08	0.83
Income ≥ 75 K	**−0.21**	**0.09**	**0.02**	−0.05	0.08	0.55	**0.19**	**0.08**	**0.02**
Time since diagnosis (years)	0.01	0.02	0.57	0.001	0.02	0.96	−0.007	0.02	0.72
Number of medical conditions	−0.02	0.04	0.56	−0.02	0.04	0.61	−0.01	0.04	0.72
Chemotherapy ever	0.04	0.09	0.67	−0.08	0.08	0.29	−0.08	0.08	0.31
Current tamoxifen use	0.06	0.11	0.56	+ 0.03	0.10	0.73	0.08	0.10	0.41
Menopausal status[a]	0.20	0.12	0.10	**0.22**	**0.11**	**0.04**	0.18	0.11	0.11
Unhappy w/body appearance	0.02	0.04	0.56	−0.02	0.03	0.60	−0.02	0.04	0.48
Global health	0.02	0.10	0.80	0.13	0.09	0.13	0.12	0.09	0.19
SF-36 energy/ fatigue	**0.007**	**0.002**	**0.002**	**0.005**	**0.002**	**0.008**	**0.006**	**0.002**	**0.003**
SF-36 physical functioning	**0.008**	**0.003**	**0.002**	**0.005**	**0.002**	**0.02**	**0.009**	**0.002**	**0.0002**

[a]The following parameters were measured: dependent variables, age at time of mailed questionnaire, ethnicity (comparison group all other ethnicities), education (comparison group: high school education or less), married/partnered (comparison group: unpartnered), income (comparison group: income <$75,000), years since diagnosis, number of medical conditions, chemotherapy ever (comparison group: did not receive chemotherapy), current tamoxifen use (comparison group: not currently using), menopausal status at time of mailed questionnaire (pre-menopausal versus peri-and post-menopausal), unhappy with body appearance, global health, energy and fatigue as measured by the SF-36, physical functioning as measured by the SF-36. Figures in bold indicate statistically significant parameters in each model.
[b]*p*-value from *F*-test for significant overall regression.
[c]*p*-value from *t*-tests of individual parameter estimates.

and 16% of HDL cholesterol at the time of the in-person sub-sample ($p < 0.0001$).

These same variables were examined for regression models of systolic and diastolic blood pressure (data not shown). The results for both systolic and diastolic blood pressure were similar and showed that blood pressure was higher for women who had higher BMIs and women who were currently taking blood pressure lowering medications (systolic blood pressure: adjusted $R^2=0.34$, $p < 0.0001$; diastolic blood pressure: adjusted $R^2=0.24$, $p < 0.0001$).

Discussion

Little is known about obesity and cardiovascular risk factors in breast cancer survivors. The purpose of this study as it was originally conceptualized was to examine the reproductive and late health outcomes in breast cancer survivors who had been diagnosed at <50 years of age. At that time, the association of cardiovascular risk with premature menopause induced by adjuvant treatment had not been elucidated. In this large cohort of younger survivors the prevalence of obesity was lower than that of a general population of age-matched women [45], and women engaged in less PA than similar samples of mid-life women [39]. Consistent with the larger literature on obesity [46–48], we found that BMI was associated with pre-existing obesity, lower income, being non-white and reporting decreased total PA. In this cohort, being unhappy with body image was also associated with a greater likelihood of obesity. Further, in examining the distribution of cardiovascular lipids levels and blood pressure in this sample of survivors, it was reassuring to find that these women did not have levels that were outside the range of normal, based on the available published literature. In addition, exploration of the predictors of lipids and blood pressure behaved in a manner consistent with the literature and did not seem to be affected by specific cancer treatments or menopausal status.

Unlike several other studies, we did not find an association of either treatment [13,22,49] or menopausal status [13,49] with BMI in our regression models. While we did observe a bivariate association between treatment and BMI, this effect was no longer significant after controlling for BMI prior to diagnosis. Goodwin et al. [13] found that the onset of menopause and the administration of chemotherapy were the sole independent predictors of weight gain (BMI) in both univariate and multivariate analyses. Our study findings likely differ from those of Goodwin et al. [13] due to substantial differences in timing of assessment. In this study, an average of approximately 6 years had passed since the time of diagnosis, whereas Goodwin et al. [13] reported findings from women just one year after the

Table 5. Factors associated with total cholesterol, LDL cholesterol and HDL cholesterol at time of in-person visit sub-sample[a]

	Total cholesterol (mg/dl) $n=285$			LDL Cholesterol (mg/dl) $n=284$			HDL cholesterol (mg/dl) $n=285$		
Model adjusted R^2 (p-value)[b]	0.09 (<0.0001)			0.14 (<0.0001)			0.16 (<0.0001)		
Parameter estimates	Coeff. (β)	Std. error	p[c]	Coeff. (β)	Std. error	p[c]	Coeff. (β)	Std. error	p[c]
Age[a]	0.19	0.51	0.71	0.37	0.44	0.40	−0.09	0.21	0.69
Ethnicity-White	2.92	4.87	0.55	1.34	4.23	0.75	0.51	2.06	0.80
College education	−2.65	7.47	0.72	−7.07	6.47	0.28	**6.36**	**3.17**	**0.05**
Income ≥75 K	8.61	4.74	0.07	7.73	4.12	0.06	0.14	2.01	0.95
Time since diagnosis (years)[a]	**2.18**	**1.00**	**0.03**	**2.23**	**0.87**	**0.01**	0.31	0.42	0.46
Chemotherapy ever	8.69	4.88	0.08	4.20	4.25	0.32	3.02	2.07	0.15
Current tamoxifen use	−9.90	6.09	0.10	−8.65	5.28	0.10	−2.04	2.58	0.43
Current cholesterol medication	−2.51	8.12	0.76	−1.28	7.16	0.86	−1.88	3.44	0.58
Menstruating	−11.91	6.38	0.06	−6.55	5.54	0.24	−3.18	2.70	0.24
At least 12 alcoholic drink in past year	−1.66	4.72	0.73	−4.63	4.09	0.26	**5.22**	**2.00**	**0.01**
Ever smoked	2.37	4.49	0.60	−1.62	3.90	0.68	−1.36	1.90	0.48
BMI kg/m^{2}[a]	0.53	0.42	0.21	**1.16**	**0.37**	**0.002**	**−1.01**	**0.18**	**<0.0001**
Leisure physical activity at time of mailed questionnaire	**−8.08**	**2.81**	**0.004**	**−6.50**	**2.43**	**0.008**	0.62	1.19	0.60

[a]The following parameters were measured: dependent variables, age at time of in-person visit, ethnicity (comparison group all other ethnicities), education (comparison group: high school education or less), married/partnered (comparison group: unpartnered), income (comparison group: income < $75,000), years since diagnosis at time of in-person visit, number of medical conditions, chemotherapy ever (comparison group: did not receive chemotherapy), current tamoxifen use (comparison group: not currently using), current use of cholesterol medication (comparison group: not currently using), menstrual status at time of in-person visit (menstruating, yes/no), alcohol consumption during the past 12 months (comparison group: < 12 alcoholic drinks), ever smoked (comparison group: never smoked), body mass index (BMI) in kg/m^2 at time of in-person visit, leisure physical activity at time of mailed questionnaire. Figures in bold indicate statistically significant parameters in each model.
[b]p-value from F-test for significant overall regression.
[c]p-value from t-tests of individual parameter estimates.

cessation of cancer treatment. In our regression models, BMI was associated with the number of years since diagnosis. This phenomenon has also been observed in longitudinal studies such as the Framingham study and others [50–52].

Obesity is a negative prognostic factor for survival among breast cancer patients whether in its relationship to breast cancer recurrence [23] or as a risk factor for cardiovascular disease [39]. In the general population of healthy women 20 years of age or older approximately two-thirds are overweight (BMI > 25kg/m^2) and of those approximately one-third are obese (BMI > 30 kg/m^2) [45]. The rates of overweight and obesity are lower in this sample of breast cancer survivors than in the general population. Epidemiologically this can be explained by the fact that pre-menopausal women who get cancer are leaner. However, we found that women who were heavier were less likely to engage in PA, and more likely to have higher blood lipids and higher blood pressure. These findings indicate that much like the general population of women, overweight survivors have increased risk factors for subsequent cardiovascular disease.

PA has been associated with a reduced risk of breast cancer, is linked to better weight maintenance, and is a modifiable behavior with the potential to influence both of these outcomes [53,54]. In these survivors, decreased total PA was associated with greater BMI, and decreased leisure time PA was associated with higher total and LDL cholesterol. Unfortunately, the ability to maintain a regular exercise regimen after breast cancer can be disrupted due to fatigue and other symptoms experienced during and after treatment [9,10,55–57]. Results from the Health, Eating, Activity and Lifestyle (HEAL) Study, a population-based, multiethnic, prospective cohort study, showed that PA levels were reduced in some women by more than 50% from pre-diagnosis to post-diagnosis depending on type of treatment [58]. Women who were most active pre-diagnosis experienced greater decreases in PA post-diagnosis compared to the least active women. Large decreases in PA were also observed among heavier patients implying a greater potential for weight gain among women who were already overweight. The cross-sectional nature of our study limits are ability to determine the causal pathway to obesity in the CAMS sample; however, PA would certainly be a potentially modifiable behavior that should be examined to decrease risk factors for breast cancer recurrence and cardiovascular disease.

This study had several limitations. The accuracy of PA and weight data may be affected due to issues related to self-report and social desirability. However, analyses with both the first National Health and Nutrition Examination Survey (NHANES I) [59] and NHANES III [60] demonstrated that most individuals can estimate both their height and weight within a reasonable margin of error. Underestimation does occur for those who are overweight [61] and the tendency to underreport past weight is usually within 15 pounds of an actual measured weight [59]. In this study there was a strong correlation between self-reported and measured height ($r = 0.952$, $p < 0.001$) and weight ($r = 0.978$, $p < 0.001$).

Despite these limitations, our results provide insight into the relationship between important lifestyle variables and how these are related to obesity among younger breast cancer survivors. Engaging in PA during the period following breast cancer treatment holds potential for reducing weight gain after treatment, decreasing obesity and improving women's physical functioning and energy levels. Risk for recurrent cancers and cardiovascular disease may also be affected by decreasing obesity and increasing physical activity. In the future, if interventions are to be developed using PA as a means of weight reduction and health promotion among breast cancer survivors, it will be important to understand what factors motivate women to engage in such activities.

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