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EPIDEMIOLOGY

Metabolic factors, anthropometric measures, diet, and physical activity in long-term breast cancer survivors: change from diagnosis and comparison to non-breast cancer controls

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Abstract
Purpose We studied metabolic factors, diabetes, and anthropometric measurements at diagnosis and long-term follow-up (LTFU), mean 12.5 years post-diagnosis, in breast cancer (BC) survivors, and compared their status at LTFU to that of age-matched women without BC. Diet and physical activity were also assessed.
Method 535 non-diabetic BC patients treated at three University of Toronto hospitals were followed prospectively; 285 surviving patients, without distant recurrence, participated in a LTFU study. A control group of 167 age-matched women without BC was recruited from a mammogram screening program at one of the hospitals. Change over time was analyzed using paired *t* tests, and comparisons between BC survivors and controls used age and education (AE)-adjusted regression models.
Results Median weight gain in BC survivors was 2.00 kg ($p < 0.0001$); BMI, glucose, insulin, homeostasis model assessment (HOMA), and total cholesterol increased modestly but significantly. Waist circumference, glucose, and triglycerides were higher in LTFU BC survivors versus controls. BC survivors had significantly greater prevalence of diabetes/pre-diabetes versus controls (33 vs. 20.4%, AE-adjusted odds ratio (OR) 1.59, $p = 0.050$). This effect was restricted to those with lower levels of physical activity (<56 metabolic equivalent (MET)-hours/week: OR 2.70 versus 0.94 for those with higher physical activity, interaction $p = 0.034$). At LTFU, BC survivors were more physically active than at diagnosis (median increase 28 MET-hours/week interquartile range −14.8 to 82), and compared to controls (median 68.2 vs. 44 MET-hours/week, $p < 0.0001$).
Conclusion The prevalence of the metabolic syndrome and diabetes/pre-diabetes was significantly higher in BC survivors than in controls group, notably in those with lower levels of physical activity. Enhanced diabetes/metabolic syndrome screening and promotion of physical activity may be warranted in BC survivors.

Keywords Breast cancer · Metabolic syndrome · Diabetes · Diet · Physical activity · Survivor · Anthropometric measurements · Lipids

Introduction

The prevalence of obesity, a modifiable health condition, has more than doubled worldwide in recent decades [1]. The obesity-associated metabolic syndrome [high triglycerides (TG), low high-density lipoprotein cholesterol (HDL), hypertension, high fasting glucose, and central obesity] has become an increasing health concern due to its association with diabetes and cardiovascular disease [2]. Obesity and the metabolic syndrome have also been associated with increased cancer risk [3].

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In breast cancer (BC), obesity has been associated with higher incidence of post-menopausal hormone receptor-positive and premenopausal triple-negative BC [4], and with poor BC outcome [3]. In a recent meta-analysis, risk of all-cause mortality was higher in BC patients with body mass index (BMI) > 30.0 mg/m^2 at BC diagnosis versus normal weight patients [relative risk (RR) 1.41, 95% confidence interval (CI) 1.29–1.53] [3]. We reported that fasting insulin at BC diagnosis was correlated with BMI ($r = 0.59$, $p < 0.001$) and with distant disease-free survival and overall survival (OS) (HR 2.05; 95% CI 1.16–3.62 and HR 2.57; 95% CI 1.18–5.59, respectively, for upper vs. lower quartile) [5]. There is growing evidence that the metabolic syndrome, also known as the insulin resistance syndrome, is associated with higher BC risk (RR, 1.47, 95% CI 1.15–1.87) [6] and BC mortality (for women aged ≥60 years (RR, 1.23; 95% CI 1.04–1.45) [7].

As the survival of BC patients improves, competing causes of mortality are of increasing relevance. Given the fact that little is known about change in metabolic status and lifestyle in BC survivors over time, we studied longitudinal change in anthropometric measurements, metabolic factors, diet, and physical activity in BC survivors and compared them to age-matched women with no history of BC (controls). Our main focus is on the prevalence of the metabolic syndrome and diabetes.

Materials and methods

Study population

535 pre- and post-menopausal women, age < 75, with early BC (T1-3 N0-1 M0), who underwent surgery at three University of Toronto Hospitals (Mount Sinai Hospital, St Michael's Hospital and Women's College Hospital), were enrolled between 1989 and 1997 and followed prospectively. Exclusion criteria included the following: inability to speak English, previous cancer (except carcinoma in situ of cervix and non-melanoma skin cancer), presence of a serious medical condition (including dyslipidemia, diabetes), or use of medications that could affect diet or lipids.

From 2005 to 2007, those who were alive without distant recurrence were re-contacted to participate in a LTFU study (Online Supplement Fig. 1): 285 agreed, 29 declined, 23 could not be located, and 198 were ineligible (123 died, 33 had distant recurrence, 28 other cancer, and 14 moved away). Most attended a hospital-based study visit; 35 were interviewed by phone due to distance from the hospital. Between 2007 and 2008, 167 sequential controls who presented for screening mammograms at one of the original participating hospitals (Mount Sinai) were enrolled. Controls were matched within 5 year strata to the current age of surviving cases—once each stratum was filled; women in that age group were no longer recruited. Exclusion criteria were history of invasive cancer at any time or undiagnosed abnormality on screening mammogram that had not been resolved as benign within 4 weeks. Participants provided written informed consent according to the Ethics Committee at participating institutions.

Measurements

BC patients provided fasting blood 4–12 weeks postoperatively (prior to adjuvant therapy) and when re-contacted for LTFU (follow-up years: mean 12.5, median 12.3, range 9.4–17.6,). Blood was not collected from LTFU patients interviewed by phone. Controls provided fasting blood during a study visit. Blood samples were collected into EDTA tubes, centrifuged immediately, and stored at −70 °C. TG, total cholesterol (TC), and HDL were analyzed using the methods of the Lipid Research Clinics [8]. Low-density lipoprotein cholesterol (LDL) was calculated using the Friedewald formula [9]. An automated Beckman-Coulter Access Immunoassay System (Beckman-Coulter Canada Inc Mississauga, Canada) was used to measure insulin; the enzymatic reference method with hexokinase was used to measure glucose.

BC patients completed a standardized questionnaire to collect demographic data, information on risk factors, and medical status at baseline and LTFU; controls completed the same questionnaires at the study visit. Trained personnel recorded weight, blood pressure, and anthropometric data after a 12-h fast. Diet over the previous year was assessed using the Block Food Frequency Questionnaire [10, 11]. Physical activity was assessed by the Stanford Five-City physical activity questionnaire [12] which recorded the number of hours spent in work-related and non-work-related moderate, hard, and very hard activities for each day of the past week. Hours of physical activity per week were summed; metabolic equivalent of task (MET) hours per week were calculated as the weighted sum of the moderate, hard, and very hard hours with weights 4, 6, and 10, respectively. Pathologic characteristics (tumor and nodal stage, grade, ER, PgR, and type of surgery) were abstracted from pathology reports. HER2 was not evaluated.

Assessment of HOMA, BMI, the metabolic syndrome, and diabetes

Homeostasis model assessment (HOMA) was calculated using a validated formula [insulin (microunits/mL) × glucose (mmol/L)/22.5] [13], and BMI as weight (kg) divided by height (m^2). The presence of the metabolic syndrome was assessed using the 2009 harmonized

definition [2] which requires at least three of the following to be present: (i) elevated waist circumference (88 cm or greater according to Canada-specific definition), (ii) TG $\geq$ 1.7 mmol/L (150 mg/dL) or drug treatment for elevated triglycerides, (iii) HDL $<$ 50 mg/dL (1.3 mmol/L) or drug treatment for reduced HDL, (iv) systolic blood pressure $\geq$130 and/or diastolic blood pressure $\geq$85 mmHg or antihypertensive drug treatment, and (v) fasting glucose $\geq$5.6 mmol/L (100 mg/dL) or drug treatment for elevated glucose. Because we used waist circumference greater $\geq$88 cm, our criteria mirrored those recommended by NEC-ATP-III [14]. The metabolic syndrome definition could not be applied to BC patients at diagnosis because of the absence of blood pressure measurements.

In accordance with the American Diabetes Association 2016 criteria, subjects were classified as having diabetes at LTFU if their fasting glucose level was $\geq$7 mmol/L or if they self-identified as diabetic, and as pre-diabetic if their fasting glucose was $\geq$5.6 mmol/L but below 7 mmol/L or if they self-identified as pre-diabetic [15] (and not also diabetic). As noted above, BC patients with known diabetes at diagnosis were excluded.

Statistical analysis

Descriptive statistics were generated for all anthropometric, metabolic, diet, and exercise variables ('the study variables'). The following transformations were used for markedly skewed study variables: $\log(x)$ for weight, waist circumference, insulin, HOMA, TG; $-1/x$ for BMI, glucose; $\text{sqrt}(x)$ for physical activity, total calories, total fat, saturated fat, dietary fiber, fruit and vegetable servings per day, and % calories from alcohol. The identity transformation was used for age, height, systolic and diastolic blood pressure; and % calories from fat, protein, and carbohydrates. Median and interquartile ranges (IQR) are reported as raw summary measures on the original scale, while transformed variables, which were more nearly normal, were used for all statistical modeling and testing.

Patient and tumor characteristics at diagnosis in BC patients were summarized, and those enrolled into the LTFU study compared to the remainder using Pearson χ^2 tests and t tests. Longitudinal change in BC survivors from diagnosis to LTFU was assessed, and the null hypothesis of no change over time tested with paired t tests.

Characteristics of the BC survivors at LTFU were compared to those of controls using Pearson χ^2 tests and t tests. Controls were slightly younger than BC survivors, and they had higher education and income. Comparisons between BC survivors at LTFU and controls for metabolic and other factors used age and education-adjusted regression models. We did not adjust for income in our primary models because lower income may be a result of the breast cancer diagnosis itself [16], and because income and education were quite highly correlated (we provided age, education, and income-adjusted results in footnotes). When adjusting, age was specified as a natural spline with two knots and education and income as in Table 2. The association of BC status (vs. control) with the metabolic syndrome and diabetes/pre-diabetes was modeled using logistic regression. The possibility of a differential effect of status by high and low values of the following variables was explored via suitable interaction terms: physical activity; total calories; % calories from fat, protein, and carbohydrates; and grams of carbohydrates (all split at the average of the BC and control group medians). Only results with significant interactions are presented.

Results

Characteristics of BC patients and controls

Enrollment of 285 (of the original 535) BC surviving patients in the LTFU cohort occurred at a mean follow-up of 12.5 years (median 12.3, range 9.4–17.6 years). As expected, those not included in the LTFU cohort had a higher baseline risk of recurrence with higher tumor and nodal stage (Table 1). Compared with those not included in the LTFU cohort, the LTFU cohort had significantly lower baseline weight (median 63.0 vs. 65.8 kg, $p = 0.0019$) and BMI (median 24.1 vs. 25.4 kg/m^2, $p = 0.0006$).

Compared to the controls, BC patients at LTFU were slightly older (median 60.9 vs. 58.1 years, $p < 0.0001$) and more likely to be post-menopausal (94 vs. 85.6%, $p = 0.0027$), see Table 2. The majority of survivors and controls were Caucasian (73% BC survivors, 81.4% controls). Controls had higher education (89.8 vs. 75.4% post-secondary, $p = 0.0002$), higher income (61.7 vs. 37.5% earned over \$75 K per year, $p < 0.0001$), and more had consumed alcohol in the past year (90.4 vs. 78.6%, $p = 0.0013$).

Change from diagnosis to LTFU in BC patients

BC survivors experienced a reduction in height (median 2.3 cm, IQR -3.5 to -0.5, $p < 0.0001$) and gained a median of 2.0 kg (IQR -1.5 to 6.2, $p < 0.0001$) over the period from diagnosis to LTFU (Table 3; Fig. 1). BMI and waist circumference increased between baseline and LTFU (24.1 vs. 25.6 kg/m^2, 78 vs. 84 cm, $p < 0.0001$). Glucose increased from a median of 5.0 at diagnosis to 5.3 mmol/L at LTFU, insulin from 33.4 to 44 pmol/L, and HOMA from 1.03 to 1.52, all $p < 0.0001$. While total cholesterol and its components HDL and LDL increased (median 4.82 vs. 5.4 mmol/L, 1.44 vs. 1.7 mmol/L and 2.8 vs. 3.2 mmol/L,

Table 1 Patient and tumor characteristics at diagnosis of breast cancer patients in the long-term follow-up (LTFU) study versus the remainder

Characteristic at diagnosis	Original Breast Cancer Cohort		p^*
	In LTFU study $N = 285$	Not in LTFU study $N = 250$	
Age (years)			0.17
Mean ± SD	49.77 ± 8.90	50.93 ± 10.57	
Median (IQR)	48.08 (43.89–55.54)	48.75 (43.13–57.46)	
Menopausal status			0.98
Pre/peri	177 (62.1%)	155 (62%)	
Post	108 (37.9%)	95 (38%)	
Height (cm)			0.16
Mean ± SD	162.35 ± 6.93	161.50 ± 6.80	
Median (IQR)	163.00 (157.40–166.00)	161.35 (157.00–166.15)	
Weight (kg)			0.0019
Mean ± SD	65.04 ± 11.73	68.65 ± 14.99	
Median (IQR)	63.00 (57.50–70.00)	65.75 (58.00–76.00)	
Body mass index			0.0006
Mean ± SD	24.69 ± 4.30	26.32 ± 5.55	
Median (IQR)	24.10 (21.58–26.99)	25.38 (22.35–29.49)	
ER/PgR			0.24
Positive/equivocal	201 (70.5%)	184 (73.6%)	
Negative	38 (13.3%)	38 (15.2%)	
Missing	46 (16.1%)	28 (11.2%)	
Initial detection			0.19
Self-reported issues	162 (56.8%)	161 (64.4%)	
Physician	29 (10.2%)	23 (9.2%)	
Mammography	94 (33.0%)	66 (26.4%)	
Tumor stage			<0.0001
T1	184 (64.6%)	113 (45.2%)	
T2	69 (24.2%)	105 (42.0%)	
T3	9 (3.2%)	18 (7.2%)	
TX	23 (8.1%)	14 (5.6%)	
Nodal status			<0.0001
Negative	220 (77.2%)	150 (60%)	
Positive	65 (22.8%)	100 (40%)	
Tumor grade			0.076
1	51 (17.9%)	26 (10.4%)	
2	118 (41.4%)	106 (42.4%)	
3	96 (33.7%)	94 (37.6%)	
Missing	20 (7.0%)	24 (9.6%)	
Surgery type			0.68
Mastectomy	67 (23.5%)	55 (22%)	
Lumpectomy	218 (76.5%)	195 (78%)	
Adjuvant chemo			0.33
No	177 (62.1%)	145 (58%)	
Yes	108 (37.9%)	105 (42%)	
Adjuvant hormones			0.81
No	175 (61.4%)	151 (60.4%)	
Yes	110 (38.6%)	99 (39.6%)	

Table 1 continued

Characteristic at diagnosis	Original Breast Cancer Cohort		p*
	In LTFU study $N = 285$	Not in LTFU study $N = 250$	
Adjuvant radiation			0.74
No	75 (26.3%)	69 (27.6%)	
Yes	210 (73.7%)	181 (72.4%)	

* p values from t tests (transformed continuous variables) or χ^2 tests (categorical variables) comparing patients in the LTFU cohort to the remainder

Table 2 Characteristics of breast cancer (BC) survivors at long-term follow-up (LTFU) and non-BC controls

Characteristic at LTFU	BC survivors at LTFU $N = 285$	Controls $N = 167$	p*
Age			<0.0001
Mean ± SD	62.28 ± 8.50	59.09 ± 7.00	
Median (IQR)	60.89 (56.70–67.23)	58.09 (54.51–63.82)	
Menstrual status			0.0027
Stopped	268 (94%)	143 (85.6%)	
Ongoing	17 (6%)	24 (14.4%)	
Years of formal education			0.0002
Some or complete high school	70 (24.6%)	17 (10.2%)	
>High school	215 (75.4%)	150 (89.8%)	
Current employment status			0.039
Full-time	105 (36.8%)	78 (46.7%)	
Part time/retired/unemployed	180 (63.2%)	89 (53.3%)	
Total family income			<0.0001
≤75,000	145 (50.9%)	48 (28.7%)	
>75,000	107 (37.5%)	103 (61.7%)	
Confidential/don't know	33 (11.6%)	16 (9.6%)	
Current marital status			0.27
Single	105 (36.8%)	53 (31.7%)	
Currently married	180 (63.2%)	114 (68.3%)	
Ethnicity			0.042
Not White	77 (27%)	31 (18.6%)	
White	208 (73%)	136 (81.4%)	
Alcohol consumption (past year)			0.0013
No	61 (21.4%)	16 (9.6%)	
Yes	224 (78.6%)	151 (90.4%)	
Smoking status			0.93
Never smoked	163 (57.2%)	98 (58.7%)	
Previous smoker	101 (35.4%)	58 (34.7%)	
Current smoker	21 (7.4%)	11 (6.6%)	

* p values from t tests (transformed continuous variables) or χ^2 tests (categorical variables) comparing BC patients at LTFU to controls

all $p < 0.0001$, respectively), triglycerides changed negligibly (median 1.04–1.12; $p = 0.054$).

BC survivors reported an increase in physical activity of 28 MET-hours/week (median 46 at diagnosis vs. 68.2 at LTFU, $p < 0.0001$). BC patients reported consuming a median of 283 fewer calories per day at LTFU than at diagnosis (from 1750 to 1531 kcal, $p < 0.0001$). Fats made up a modestly smaller percentage of the total calories at LTFU (35.7%) than at diagnosis (38.2%), $p < 0.0001$, with both protein and carbohydrates increasing modestly (from 14.5 to 15.6% and from 44.9 to 48.5%, $p < 0.0001$, respectively). Grams of fat and saturated fats consumed per

Table 3 Change from diagnosis to long-term follow-up (LTFU) in breast cancer (BC) survivors: anthropometric, metabolic, diet, and physical activity measurements

	N^a	Median (Interquartile range)			p^*
		BC survivors at diagnosis	BC survivors at LTFU	Change	
Age (years)	285	48.08 (43.89–55.54)	60.89 (56.70–67.23)	12.29 (11.09–13.61)	–
Height (cm)	284	163.00 (157.40–166.00)	160.00 (155.50–164.50)	−2.30 (−3.50 to −0.50)	<0.0001
Weight (kg)	284	63.10 (57.40–70.00)	65.10 (58.40–74.35)	2.00 (−1.45 to 6.22)	<0.0001
Body mass index	284	24.09 (21.58–27.00)	25.63 (22.85–29.24)	1.50 (0.03–2.91)	<0.0001
Waist circumference (cm)	219	78.00 (72.50–84.65)	83.50 (77.20–91.55)	5.00 (1.95–9.25)	<0.0001
Glucose (mmol/L)	220	5.00 (4.70–5.30)	5.30 (4.90–5.80)	0.30 (0.10–0.80)	<0.0001
Insulin (pmol/L)	228	33.35 (25.68–45.10)	44.00 (33.00–71.25)	12.2 (0.90–28.55)	<0.0001
HOMA	217	1.03 (0.76–1.39)	1.52 (1.07–2.46)	0.50 (0.10–1.14)	<0.0001
Total cholesterol (mmol/L)	230	4.82 (4.23–5.33)	5.40 (4.80–6.00)	0.70 (−0.03 to 1.30)	<0.0001
TG (mmol/L)	230	1.04 (0.80–1.42)	1.12 (0.83–1.48)	0.04 (−0.23 to 0.35)	0.054
HDL (mmol/L)	230	1.44 (1.27–1.69)	1.70 (1.40–2.00)	0.21 (0.00–0.47)	<0.0001
LDL (mmol/L)	229	2.80 (2.27–3.27)	3.20 (2.60–3.70)	0.42 (−0.25 to 1.02)	<0.0001
Physical activity (MET-h/week)	278	46.00 (12.00–90.00)	68.25 (32.45–133.75)	28.00 (−14.75 to 82.00)	<0.0001
Total calories (kcal)	240	1749.75 (1376.55–2148.22)	1530.95 (1170.82–1868.32)	−282.60 (−603.97 to 97.72)	<0.0001
%Fat calories	240	38.15 (34.27–42.95)	35.74 (30.61–40.91)	−2.60 (−8.82 to 2.54)	<0.0001
%Protein calories	240	14.50 (13.08–16.20)	15.61 (13.93–17.39)	1.04 (−1.08 to 2.96)	<0.0001
%Carbohydrate calories	240	44.90 (40.50–48.82)	48.53 (42.42–55.44)	3.19 (−1.56 to 10.30)	<0.0001
%Alcohol calories	240	1.10 (0.10–4.12)	1.15 (0.20–4.80)	0.10 (−0.52 to 1.43)	0.0059
Carbohydrates/day (g)	240	193.55 (156.70–238.57)	178.65 (138.88–227.72)	−17.95 (−60.38 to 30.87)	0.0032
Total fat/day (g)	240	76.35 (55.68–96.82)	59.80 (43.25–78.68)	−13.90 (−35.10 to 3.50)	<0.0001
Saturated fat/day (g)	240	23.90 (18.27–31.78)	15.90 (11.80–21.82)	−7.20 (−14.63 to −2.00)	<0.0001
Dietary fiber/day (g)	240	12.90 (9.78–17.05)	17.25 (12.45–23.02)	3.80 (−0.40 to 8.82)	<0.0001
Fruit and vegetable servings/day	240	5.44 (3.96–6.89)	5.60 (3.80–7.50)	0.18 (−1.51 to 2.06)	0.30

TG triglycerides

[a] Number of patients with measurements at both time points

* p value from paired t tests using transformed variables

day declined between diagnosis and LTFU (from 76.4 to 59.8 g, $p < 0.0001$ and 23.9 to 15.9 g, $p < 0.0001$, respectively).

Status of long-term BC survivors compared with controls

Despite exclusion of BC patients with diabetes at study entry, 94 of 285 BC survivors (33%) had diabetes or pre-diabetes at LTFU [15] (Table 4). Of the remaining 191, 145 did not have diabetes/pre-diabetes and 46 (mainly those who participated by phone) had missing information either for glucose or self-reported medical conditions (but not both), the available information not being indicative of diabetes/pre-diabetes. Combining these into an 'absent' group gives a conservative (low) estimate of diabetes/pre-diabetes prevalence. In controls, 34 of 167 (20.4%) were diabetic or pre-diabetic. After age and education (AE) adjustment, the odds ratio (OR) for diabetes/pre-diabetes in BC patients versus controls was 1.59, 95% CI 0.99–2.53, $p = 0.05$. The odds ratio differed significantly by level of physical activity (interaction $p = 0.034$): OR = 2.70, 95% CI 1.33–5.52 for lower activity levels vs. OR = 0.94, 95% CI 0.50–1.78 for higher activity levels. In BC survivors, chemotherapy use was not significantly associated with diabetes/pre-diabetes ($p = 0.13$). Diabetes by itself was present in 6.7% of BC survivors versus 3.6% of controls, and the AE-adjusted odds ratio was 1.44, 95% CI 0.54–3.82, $p = 0.45$. Due to the low number of events it could not be analyzed further.

Based on the harmonized metabolic syndrome criteria, at LTFU, 63 of 285 BC patients (22.1%) qualified as having metabolic syndrome (Table 4). For the remaining 222, the metabolic syndrome was absent in 175 and 47 had missing information. Similar to the diabetes analysis, we assumed that metabolic syndrome was absent for these 47 patients for a conservative prevalence estimate. In controls, 11.4% met the criteria for the metabolic syndrome. After AE adjustment, the OR for BC patients versus controls was 1.73, 95% CI 0.97–3.08, $p = 0.056$. The OR differed

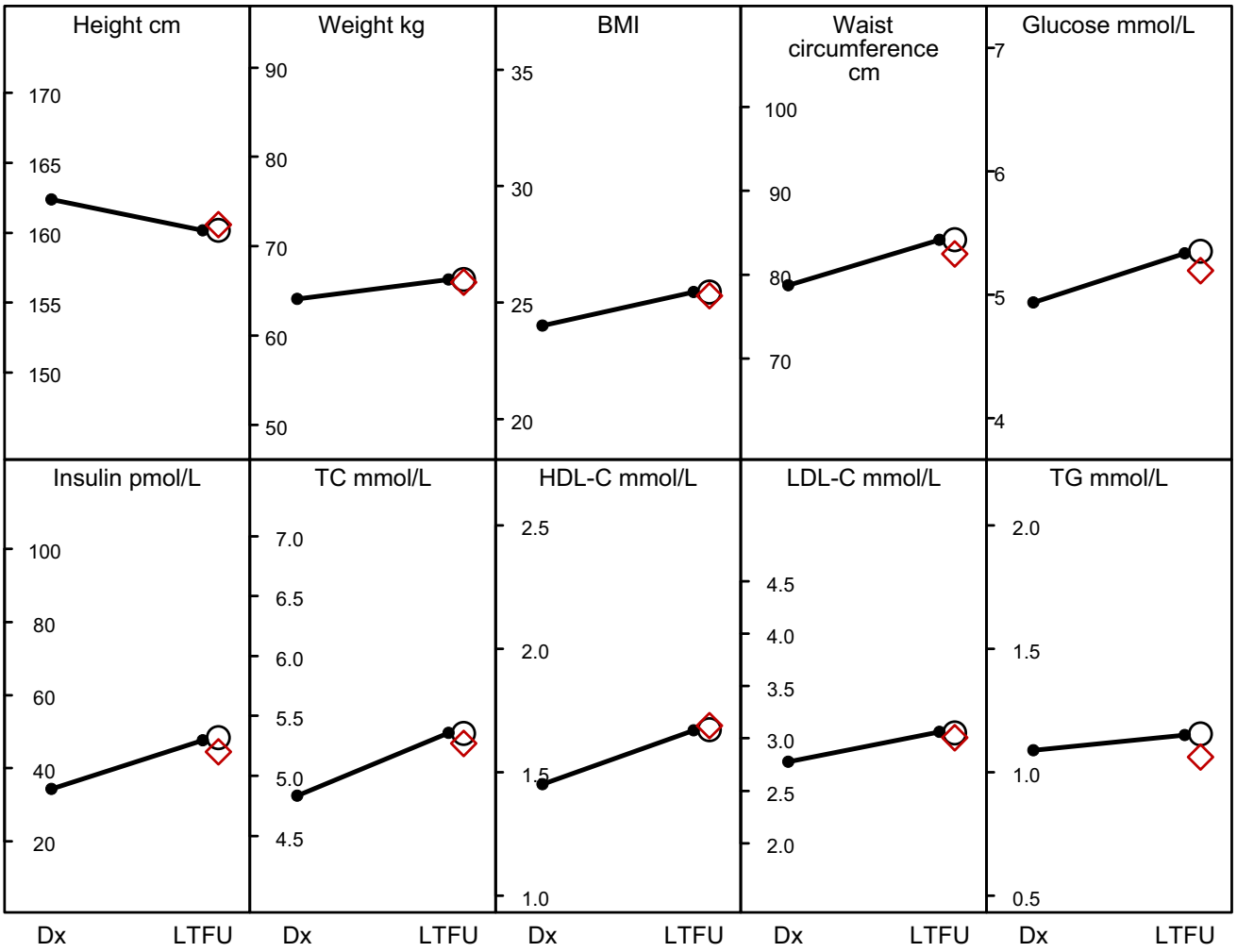

Fig. 1 Change in breast cancer (BC) survivors and status at long-term follow-up (LTFU) versus non-BC controls: comparison of anthropometric and metabolic measurements. The slope of each *black line* indicates the mean change from diagnosis (*Dx*) to LTFU in the BC cohort and the circle is their mean level at LTFU. The *diamond* gives the age and education-adjusted mean for the controls. Means were obtained on the transformed scale and back-transformed for display purposes

significantly by level of physical activity (interaction $p = 0.035$): OR = 3.25, 95% CI 1.37–7.75 for lower activity levels versus 0.98, 95% CI 0.45–2.16 for higher activity levels. Use of adjuvant chemotherapy was not significantly associated with metabolic syndrome ($p = 0.15$).

In terms of the components of the metabolic syndrome, AE-adjusted waist circumference, triglycerides, glucose, and diastolic blood pressure were slightly but significantly higher in BC survivors versus controls (84 vs. 80 cm, $p = 0.034$; 1.12 vs. 0.94 mmol/L, $p = 0.018$; 5.3 vs. 5.1 mmol/L, $p = 0.019$; 78 vs. 74 mmHg, $p = 0.033$; respectively) (Table 5; Fig. 1). There was little difference in AE-adjusted LDL, HDL, and insulin. AE-adjusted weight, height, and BMI were also similar at LTFU between BC patients and controls.

After AE adjustment, there were few differences in diet in long-term survivors versus controls, apart from slightly lower fiber intake per day (median 17.4 vs. 18.7 g, $p = 0.04$) as well as a smaller percentage of calories from alcohol (1.1 vs. 2.5%, $p = 0.0055$). BC patients at LTFU reported being more physically active than controls (median 68.2 vs. 44 MET-h/week of total physical activity, $p < 0.0001$).

Discussion

The long-term BC survivors in this study represent a selected population who were alive and distant recurrence-free. We have shown that as these survivors aged, BMI, weight, key metabolic factors, and anthropometric measures

Table 4 Prevalence of the metabolic syndrome and diabetes/pre-diabetes in long-term breast cancer (BC) survivors and controls

	Raw prevalence		Age and education-adjusted logistic regression model		
	BC survivors at LTFU[a]	Controls	OR[b]	95% CI	P[c]
Diabetes or pre-diabetes	94/285 (33%)	34/167 (20.4%)	1.59	0.99–2.53	0.050
By physical activity[d]			Interaction $p = 0.034$		
<56 MET-h/week	41/112 (36.6%)	14/94 (14.9%)	2.70	1.33–5.52	0.0049
56+ METS-h/week	51/168 (30.4%)	20/72 (27.8%)	0.94	0.50–1.78	0.86
Metabolic syndrome	63/285 (22.1%)	19/167 (11.4%)	1.73	0.97–3.08	0.056
By physical activity[d]			Interaction $p = 0.035$		
<56 MET-h/week	32/112 (28.6%)	8/94 (8.5%)	3.25	1.37–7.75	0.0049
56+ METS-h/week	30/168 (17.9%)	11/72 (15.3%)	0.98	0.45–2.16	0.96

A differential effect by physical activity was found after examining age and education-adjusted interactions between status (BC patient or control) and physical activity; total calories; % calories from fat, protein, and carbohydrates; and grams of carbohydrates

[a] BC patients with missing information about their diabetes/pre-diabetes or metabolic syndrome status (46 and 47 patients, respectively) were classified as negative, giving conservatively low estimates of their prevalences

[b] Age and education-adjusted odds ratio for BC patients versus controls

[c] When further adjusted for income, the main effect p value for diabetes/pre-diabetes increased from 0.05 to 0.10 and for the metabolic syndrome from 0.056 to 0.14. Other p values including interaction p values did not change materially

[d] Physical activity levels were available for 280 BC survivors and 166 controls

modestly increased, and, as expected with increasing age, their height decreased (median 2 cm). At LTFU (vs. diagnosis), they had modestly lower fat and carbohydrate intake and higher protein intake. Compared to controls, BC survivors at LTFU had slightly higher waist circumference, glucose, and triglycerides. The lack of difference between BC survivors at LTFU versus controls for many study variables may suggest that some changes seen in BC survivors reflected normal aging. Survivors had lower alcohol intake compared to controls, which could potentially reflect a recognition that alcohol is associated with BC (we do not have data to investigate this hypothesis).

The apparent increase in physical activity over time in BC cases could reflect decreased postoperative physical activity during baseline measurement (4–12 weeks postoperatively) or a true increase in activity; it is possible a BC diagnosis prompts more focused attention on lifestyle and controllable determinants of health. The finding of higher physical activity in BC cases at LTFU versus controls was not expected and requires replication.

At LTFU, BC patients had greater prevalence of pre-diabetes/diabetes compared to controls, despite exclusion of BC patients with known diabetes at diagnosis. At LTFU, BC patients also had greater prevalence of the metabolic syndrome. Both these associations were present only in women with low levels of physical activity, raising the possibility that enhanced physical activity may prevent the development of diabetes/pre-diabetes or the metabolic syndrome (with its associated increased risk of cardiovascular disease) in BC survivors. If this is confirmed, physical activity interventions may also reduce risk of associated major co-morbidities (such cardiovascular disease) and non-BC cause of death and may have the potential to enhance quality and quantity of life in BC survivors.

The occurrence of diabetes after BC diagnosis has been investigated previously. One population-based study found that 9.7% of post-menopausal BC survivors developed diabetes over a mean follow-up of 5.8 years; risk was highest in those who received adjuvant chemotherapy (HR 1.24 95% CI 1.12–1.38 in the first 2 years after chemotherapy) [17]. Bordeleau et al. observed a doubled risk of diabetes in BRCA carriers diagnosed with BC (vs. carriers without cancer) in the 15-year period after diagnosis (RR 2.0; 95% CI 1.4–2.8; $p = 0.0001$) [18]. These findings may reflect an association of insulin resistance with BC risk or an impact of BC treatment (e.g., chemotherapy, dexamethasone, and hormone therapy) on risk of diabetes. In one study, patients receiving tamoxifen (vs. no tamoxifen) had a higher incidence of diabetes over a mean follow-up of 5.2 years (OR 1.24; 95% CI 1.08–1.42; $p = 0.002$) [19]. Adjuvant BC chemotherapy has also been associated with transient hyperglycemia [20], an increase in the metabolic syndrome and dysglycemia [21]. However, we did not observe an independent association of diabetes/pre-diabetes or the metabolic syndrome with adjuvant chemotherapy use, suggesting chemotherapy use was not primarily responsible for our observed associations.

Our study has limitations. In BC patients, we conducted measurements only at diagnosis and LTFU. It is not known whether anthropometric measurements, metabolic factors, diet, or physical activity varied between these times. Future studies should consider measurement at additional time

Table 5 Breast cancer (BC) survivors at long-term follow-up (LTFU) versus non-BC controls: comparison of anthropometric, metabolic, diet, and physical activity measurements

	Unadjusted median (interquartile range)				AE-adjusted p*
	N[a]	BC cohort at LTFU	N[a]	Controls	
Age (years)	285	60.89 (56.70–67.23)	167	58.09 (54.51–63.82)	–
Height (cm)	284	160.00 (155.50–164.50)	167	161.00 (157.00–166.00)	0.41
Weight (kg)	284	65.10 (58.40–74.35)	167	63.90 (59.00–72.85)	0.53
Body mass index (BMI)	284	25.63 (22.85–29.24)	167	24.48 (22.35–27.10)	0.36
Waist circumference (cm)	281	83.60 (76.20–92.00)	167	79.50 (73.70–87.40)	0.034
Blood pressure systolic (mmHg)	270	122.00 (112.00–132.00)	167	120.00 (110.00–124.00)	0.11
Blood pressure diastolic (mmHg)	271	78.00 (70.00–82.00)	167	74.00 (70.00–80.00)	0.033
Glucose (mmol/L)	241	5.30 (4.90–5.80)	167	5.10 (4.80–5.40)	0.019
Insulin (pmol/L)	241	44.00 (33.00–73.00)	167	42.00 (29.50–56.00)	0.12
HOMA	241	1.53 (1.07–2.66)	167	1.38 (0.91–1.89)	0.063
Total cholesterol (mmol/L)	235	5.40 (4.80–6.00)	164	5.40 (4.80–6.10)	0.59
TG (mmol/L)	235	1.12 (0.84–1.48)	164	0.94 (0.77–1.33)	0.018
HDL (mmol/L)	235	1.70 (1.40–2.00)	164	1.70 (1.40–2.00)	0.28
LDL (mmol/L)	235	3.10 (2.60–3.60)	164	3.10 (2.50–3.60)	0.68
Physical activity (MET-h/week)	280	68.25 (32.55–134.50)	166	44.00 (26.00–84.75)	<0.0001
Total calories (kcal)	248	1520.75 (1172.15–1859.60)	159	1511.90 (1197.50–1887.00)	0.82
%Fat calories	248	35.94 (30.61–41.42)	159	36.07 (30.54–39.70)	0.55
%Protein calories	248	15.64 (13.94–17.53)	159	16.17 (14.24–17.68)	0.29
%Carbohydrate calories	248	48.48 (42.42–55.44)	159	47.71 (43.04–52.78)	0.49
%Alcohol calories	248	1.10 (0.20–4.73)	159	2.50 (0.50–6.95)	0.0055
Carbohydrates/day (g)	248	178.05 (138.60–225.95)	159	179.10 (142.25–230.35)	0.95
Total fat/day (g)	248	60.45 (43.45–78.12)	159	58.40 (44.60–77.70)	0.86
Saturated fat/day (g)	248	15.90 (11.80–21.63)	159	15.40 (11.40–21.65)	0.54
Dietary fiber/day (g)	248	17.40 (12.65–23.10)	159	18.70 (13.45–26.30)	0.04
Fruit and vegetable servings/day	248	5.60 (3.80–7.55)	159	5.80 (4.15–7.95)	0.40

TG triglycerides

[a] Number of patients with non-missing data

* p values for age- and education (AE)-adjusted differences between BC patients at LTFU and controls from linear regression models, using transformed variables. When further adjusted for income, the p values for waist circumference, glucose, and TG increased to 0.21, 0.065, and 0.069, respectively; other p values were not materially affected

points. The BC population in our study was largely Caucasian and middle class, and controls were slightly younger (the provincial screening program offered routine screening only to age 69) and more highly educated. The control group was enrolled from those presenting for screening mammograms; this group may be more likely to engage in healthy behavior, representing a potential bias. Additionally, controls were not followed over time. The ideal study design would have used a prospective case–cohort design; future studies should identify cases and controls and follow them prospectively.

In summary, the metabolic status of long-term BC survivors modestly deteriorated over time (potentially reflecting normal aging, at least in part) and at LTFU, metabolic status was worse compared to a control group, notably in those who were physically inactive. Importantly, a significantly higher prevalence of diabetes/pre-diabetes was observed in BC survivors compared to controls. Our results have implications for the overall health of BC patients as diabetes is a major cause of morbidity and mortality, while both diabetes and the metabolic syndrome are associated with higher risk of cardiovascular disease. Further studies should attempt to confirm these findings. Enhanced diabetes and metabolic syndrome screening as well as lifestyle modification programs should be studied as means to improve outcomes in BC survivors.

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Compliance with ethical standards

Conflict of interest The author(s) declare that they have no competing interests.

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