International Journal of Epidemiology, 2018, 987–997
doi: 10.1093/ije/dyy039
Advance Access Publication Date: 13 March 2018
Original article

Miscellaneous

Prospective evaluation of body size and breast cancer risk among *BRCA1* and *BRCA2* mutation carriers

Shana J Kim,[1] Tomasz Huzarski,[2] Jacek Gronwald,[2] Christian F Singer,[3] Pål Møller,[4,5,6] Henry T Lynch,[7] Susan Armel,[8] Beth Y Karlan,[9] William D Foulkes,[10] Susan L Neuhausen,[11] Leigha Senter,[12] Andrea Eisen,[13] Charis Eng,[14] Seema Panchal,[15] Tuya Pal,[16] Olufunmilayo Olopade,[17] Dana Zakalik,[18] Jan Lubinski,[2] Steven A Narod[1,19] and Joanne Kotsopoulos[1,19]* for the Hereditary Breast Cancer Clinical Study Group

[1]Women's College Research Institute, Women's College Hospital, Toronto, Ontario, Canada, [2]Department of Genetics and Pathology, International Hereditary Cancer Center, Pomeranian Medical University, Szczecin, Poland, [3]Department of Obstetrics and Gynecology and Comprehensive Cancer Center, Medical University of Vienna, Vienna, Austria, [4]Inherited Cancer Research Group, Department for Medical Genetics, Oslo University Hospital, Oslo, Norway, [5]Department of Tumor Biology, Institute of Cancer Research, Oslo University Hospital, Oslo, Norway, [6]Surgical Center for Hereditary Tumors, HELIOS University Clinic Wuppertal, University Witten-Herdecke, Wuppertal, Germany, [7]Hereditary Cancer Center, Creighton University School of Medicine, Omaha, NE, USA, [8]Department of Gynecologic Oncology, Princess Margaret Cancer Center, University Health Network, Toronto, Ontario, Canada, [9]Women's Cancer Program, Division of Gynecologic Oncology, Cedars-Sinai Medical Center, Los Angeles, CA, USA, [10]Program in Cancer Genetics, Department of Oncology and Human Genetics, McGill University, Montréal, Quebec, Canada, [11]Department of Population Sciences, Beckman Research Institute of City of Hope, Duarte, CA, USA, [12]Division of Human Genetics, Ohio State University Medical Center, Comprehensive Cancer Center, Columbus, OH, USA, [13]Odette Cancer Centre, Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada, [14]Genomic Medicine Institute, Center for Personalized Genetic Healthcare, Cleveland Clinic, Cleveland, OH, USA, [15]Mount Sinai Hospital, Toronto, Ontario, Canada, [16]Vanderbilt-Ingram Cancer Center/Vanderbilt University Medical Center, Nashville, TN, USA, [17]Department of Medicine, University of Chicago, Chicago, IL, USA, [18]Cancer Genetics Program, Beaumont Hospital, Royal Oak, MI, USA and [19]Dalla Lana School of Public Health, University of Toronto, Toronto, Ontario, Canada

*Corresponding author. Women's College Research Institute, Women's College Hospital, 76 Grenville St., 6th Floor, Toronto, ON, M5S 1B2, Canada. E-mail: joanne.kotsopoulos@wchospital.ca

Editorial decision 13 February 2018; Accepted 26 February 2018

Abstract

Background: Although evidence suggests that larger body size in early life confers life-long protection from developing breast cancer, few studies have investigated the

relationship between body size and breast cancer risk among *BRCA* mutation carriers. Therefore, we conducted a prospective evaluation of body size and the risk of breast cancer among *BRCA* mutation carriers.

Methods: Current height and body mass index (BMI) at age 18 were determined from baseline questionnaires. Current BMI and weight change since age 18 were calculated from updated biennial follow-up questionnaires. Cox proportional hazards models were used to estimate the hazard ratio (HR) and 95% confidence interval (CI).

Results: Among 3734 *BRCA* mutation carriers, there were 338 incident breast cancers over a mean follow-up of 5.5 years. There was no association between height, current BMI or weight change and breast cancer risk. Women with BMI at age 18 $\geq$22.1 kg/m^2 had a decreased risk of developing post-menopausal breast cancer compared with women with a BMI at age 18 between 18.8 and 20.3 kg/m^2 (HR 0.49; 95% CI 0.30–0.82; $P = 0.006$). BMI at age 18 was not associated with risk of pre-menopausal breast cancer.

Conclusions: There was no observed association between height, current BMI and weight change and risk of breast cancer. The inverse relationship between greater BMI at age 18 and post-menopausal breast cancer further supports a role of early rather than current or adulthood exposures for *BRCA*-associated breast cancer development. Future studies with longer follow-up and additional measures of adiposity are necessary to confirm these findings.

Key words: BMI, body size, breast cancer, BRCA, hereditary cancer

Key Messages

- Women with a body mass index (BMI) at age 18 $\geq$22.1 kg/m^2 had a decreased risk of developing post-menopausal breast cancer compared with women with a BMI at age 18 between 18.8 and 20.3 kg/m^2.
- There was no observed association between height, current BMI or weight change and breast cancer risk.
- Findings from this study further support a role of early rather than current or adulthood exposures in *BRCA*-associated breast cancer development.

Introduction

The relationship between anthropometric parameters such as height, body mass index (BMI) and body weight and subsequent breast cancer risk has been examined extensively among women in the general population. Collectively, the evidence suggests that a larger body size (measured by BMI or body weight), when compared with normal body size, in adolescence and early adulthood confers lifelong protection from developing breast cancer.[1–6] Furthermore, menopausal status is an established modifier: greater body size is associated with a decreased risk of pre-menopausal breast cancer, but an increased risk of post-menopausal breast cancer.[6] The possible underlying mechanisms mediating the relationship between obesity and breast cancer development include the metabolic consequences of obesity (e.g. hyperinsulinemia, insulin resistance), elevated levels of circulating growth factors (e.g. glucose, IGF-1), as well as the impact of endogenous sex hormone levels (e.g. estrogen, testosterone).[7–9]

Few studies have investigated the impact of body size on breast cancer risk among women with an inherited *BRCA1* or *BRCA2* mutation.[10–14] In the largest study conducted to date, which included 1073 matched pairs of *BRCA* mutation carriers, we previously reported that weight loss of at least 10 pounds in early adulthood (between the ages of 18 and 30) was associated with a 53% reduction in breast cancer diagnosed between ages 30 and 40 years ($P = 0.005$).[12] There was no association between weight loss and breast cancer diagnosed after age 40 years. Other reports of body size and breast cancer in this high-risk population have been limited by retrospective study designs and by small sample sizes, yet suggest that

maintenance of a healthy body weight, particularly in early adult life, may be associated with a decreased risk.[10–14]

BRCA mutation carriers face high lifetime risks of developing breast cancer.[15] Given the high penetrance of these mutations, the opportunity for prevention is of extreme importance. Furthermore, the early age at *BRCA*-breast cancer diagnosis (typically between ages 30 and 50 years),[16] along with our earlier report of a protective role of weight loss in early adulthood, suggests that body size in early life may impact *BRCA*-associated breast cancer risk.[12] Thus, we conducted the first prospective evaluation of height, BMI at age 18, current BMI and weight change since age 18 and breast cancer risk among women with a *BRCA1* or *BRCA2* mutation.

Methods

Study population

Eligible study subjects were identified from a multicenter, longitudinal cohort study of *BRCA1* and *BRCA2* mutation carriers from 80 centres in 17 countries. These women sought genetic testing for a *BRCA1* or *BRCA2* mutation because of a personal or family history of breast or ovarian cancer. Mutation detection was conducted using a range of techniques, but all nucleotide sequences were confirmed by direct sequencing of DNA. The study was approved by the institutional ethics review boards of the host institutions and all study subjects provided written informed consent.

Data collection

All study subjects completed a baseline questionnaire at the time of study enrolment and follow-up questionnaires every 2 years thereafter. Baseline questionnaires were either mailed to each study participant or administered over the phone by a genetic counsellor or research assistant at the time of genetic testing. The baseline questionnaire collected information on family and personal medical histories, as well as various reproductive, hormonal and lifestyle factors. Participants also reported their current height (feet and inches), current weight (pounds) and their weight at age 18 (pounds). Follow-up questionnaires were administered biennially to update information on relevant covariates (e.g. parity and menopausal status), current weight (pounds) and incident disease. Information on incident breast cancers, including hormone receptor status, was collected from follow-up questionnaires and pathology records. For this analysis, incident breast cancers consisted of first primary invasive breast cancers.

Assessment of anthropometric measures

Height was converted to metres (m) and weight was converted to kilogrammes (kg). BMI at age 18 was calculated as weight at age 18 in kilogrammes divided by height in metres squared (kg/m^2). Height and BMI at age 18 were analysed as fixed exposures that were not updated over time. Current BMI was calculated using current weight values that were updated at each follow-up questionnaire cycle and analysed as a time-varying exposure. Weight change since age 18 was calculated as the difference between current weight and weight at age 18, and was also analysed as a time-varying exposure. Weight loss or gain of $\leq$2 kg since age 18 was considered a stable weight based on cut-offs previously reported in the literature.[17,18]

Study subjects available for analysis

For the current study, 15 525 potentially eligible *BRCA* mutation carriers were identified. Subjects were excluded if they had a previous diagnosis of any type of cancer ($n = 8624$), had undergone a prophylactic bilateral mastectomy prior to completion of the baseline questionnaire ($n = 1055$), did not complete at least one follow-up questionnaire ($n = 1888$), were missing the date of breast cancer diagnosis ($n = 4$), were missing *BRCA* mutation type ($n = 24$), were missing data on parity ($n = 32$) or missing values for height, BMI at age 18, current BMI and weight change at age 18 ($n = 149$). Subjects with a BMI of <15 kg/m^2 were excluded from our analyses ($n = 15$). After these exclusions, a total of 3734 subjects were available for the analysis, with 3718 subjects with data available for the analysis for height, 3381 for BMI at age 18, 3576 for current BMI and 3318 for weight change since age 18.

Statistical analysis

Anthropometric exposures including height, BMI at age 18 and current BMI were categorized into quartiles based on the distribution of the entire cohort at the beginning of the study period. The categories for weight change since age 18 were based on those previously used in the literature.[17,18] We utilized the second quartile as the reference group for all the analyses, since this quartile most closely represents a healthy or stable weight. In the event that weight was missing for a questionnaire cycle, the weight from one cycle prior was carried forward for only one cycle, with any additional cycles considered as missing.

Participants were followed from the date of completion of the baseline questionnaire until either the date of a breast cancer diagnosis, date of prophylactic mastectomy, date of death or date of completion of their last follow-up questionnaire. The follow-up period of this analysis was from the date of baseline until 15 March 2017.

Cox proportional hazards models were used to estimate the hazard ratio (HR) and 95% confidence interval (CI) of breast cancer with each anthropometric exposure using days of follow-up as the time variable. The simple model was adjusted for age at baseline (continuous), whereas the multivariable model additionally adjusted for *BRCA* mutation type (*BRCA1* or *BRCA2*), country of residence (North America, Poland or other), parity (ever or never had a live full-term birth; time-dependent) and menopausal status (pre-menopausal or post-menopausal; time-dependent). Study subjects who carried both a *BRCA1* and *BRCA2* mutation were categorized as *BRCA1* mutation carriers ($n = 9$). Tests for trend were conducted by assigning the median value of each quartile and modelling them as a continuous variable.

Analyses were stratified a priori by *BRCA* mutation type (*BRCA1* or *BRCA2*) and menopausal status (pre-menopausal or post-menopausal at censoring/event; time-dependent), as menopausal status is a known modifier of body weight and breast cancer risk among women in the general population. Participants were categorized as post-menopausal if they had stopped menstruating for at least a year due to natural causes, had a bilateral oophorectomy with or without hysterectomy or had radiation- or chemotherapy-induced menopause. *BRCA* mutation type or menopausal status was removed as a covariate from the multivariable model in the analysis stratified by *BRCA* mutation type and menopausal status, respectively. Additional post-hoc stratified analyses were performed to investigate potential effect modification of estrogen receptor status [estrogen receptor-positive (ER+) or estrogen receptor-negative (ER-)], age at breast cancer diagnosis (<50 or ≥50 years) and cause of menopause (natural or surgical) and breast cancer risk. Weight change since age 18 was additionally stratified by BMI at age 18 (<21 or ≥21 kg/m^2) to investigate whether low or high BMI at age 18 influenced the relationship between weight change since age 18 and breast cancer risk. The statistical significance of interaction terms was determined using the likelihood ratio test.

All analyses were conducted using the SAS statistical package, version 9.4 software (SAS Institute, Cary, NC, USA).

Results

Subject characteristics

The baseline characteristics of the participants by quartile of current BMI are summarized in Table 1. Compared with study subjects with lower BMIs, subjects with higher BMIs were older, more likely to reside in North America and were less likely to be nulliparous. Participants with higher BMI were also more likely to be post-menopausal, with a greater proportion undergoing natural menopause vs surgical or medical menopause, and had a later age at menopause. Lastly, participants with higher BMI were more likely to have higher BMI at age 18 and experienced greater weight gain since age 18 compared with those with lower BMI. The median height of the participants was 1.65 m (range 1.27–2.08 m) and the median BMI at age 18 was 20.2 kg/m^2 (15–44.4 kg/m^2). At baseline, the median BMI among all participants was 23.2 kg/m^2 (15.6–63.8 kg/m^2) and the median weight change since age 18 was 7.0 kg (–38.5–88.5 kg).

Over a mean follow-up time of 5.5 (± 3.6) years, there were a total of 338 incident primary invasive breast cancers diagnosed, including 188 cases of pre-menopausal breast cancer and 150 cases of post-menopausal breast cancer. During the follow-up period, 446 women went through menopause, with the average age at natural menopause being 49.2 years and at surgical menopause being 41.8 years.

BMI at age 18, current BMI and risk of breast cancer

BMI at age 18, current BMI and risk of breast cancer among *BRCA* mutation carriers are presented in Table 2. BMI at age 18 was not associated with breast cancer risk among all women combined (≥22.1 kg/m^2 vs ref HR 0.80; 95% CI 0.58–1.10; $P = 0.16$) or by *BRCA* mutation type. Similarly, current BMI was not associated with the risk of breast cancer among all women (≥22.1 kg/m^2 vs ref HR 0.81; 95% CI 0.60–1.11; $P = 0.20$) or by *BRCA* mutation type.

The association between BMI at age 18 and current BMI with breast cancer was further stratified by menopausal status (Table 3). Women with a BMI at age 18 of ≥22.1 kg/m^2 had a 51% decreased risk of developing post-menopausal breast cancer compared with women in the reference category (HR 0.49; 95% CI 0.30–0.82; $P = 0.006$). There was no evidence for a linear relationship (P-trend = 0.34). BMI at age 18 was not associated with risk of pre-menopausal breast cancer (HR 1.14; 95% CI 0.75–1.73; $P = 0.56$). Current BMI was not associated with risk of pre- or post-menopausal breast cancer.

The association between BMI at age 18, as well as current BMI and risk of breast cancer, did not vary by ER status, by age at breast cancer diagnosis or by type of menopause (P-interaction ≥ 0.38) (Supplementary Tables S1 and S2, available as Supplementary data at *IJE* online).

Weight change since age 18 and risk of breast cancer

Weight change since age 18 was not associated with risk of breast cancer among all women (>25.0 kg weight gain vs

Table 1. Baseline characteristics of *BRCA* mutation carriers by current BMI[a]

Characteristic	Current BMI (kg/m^2)			
	<20.9 ($n=889$)	20.9 to <23.3 ($n=860$)	23.3 to <26.6 ($n=858$)	>26.6 ($n=886$)
Age, mean (SD), y	32.4 (10.4)	37.5 (11.6)	41.0 (11.6)	43.8 (12.3)
Mutation type[b]				
BRCA1	739 (83.1)	674 (78.4)	664 (77.4)	660 (74.5)
BRCA2	150 (16.9)	186 (21.6)	194 (22.6)	226 (25.5)
Country				
North America	349 (39.3)	414 (48.1)	433 (50.5)	487 (55.0)
Poland	493 (55.5)	383 (44.5)	373 (43.5)	362 (40.9)
Other	47 (5.3)	63 (7.3)	52 (6.1)	37 (4.2)
Age at menarche, mean (SD), y	13.2 (1.5)	13.2 (1.4)	13.1 (1.6)	12.8 (1.6)
Nulliparous	413 (46.5)	291 (33.8)	196 (22.8)	170 (19.2)
Menopausal status[c]				
Pre-menopausal	757 (85.2)	664 (77.2)	575 (67.0)	527 (59.5)
Post-menopausal	132 (14.9)	196 (22.8)	283 (33.0)	359 (40.5)
Menopause cause				
Natural	49 (16.1)	102 (22.7)	165 (30.1)	198 (31.4)
Surgical	240 (78.7)	331 (73.6)	368 (67.2)	416 (66.0)
Medication/radiotherapy	16 (5.3)	17 (3.8)	15 (2.7)	16 (2.5)
Age at menopause, mean (SD), y	43.1 (7.2)	43.9 (7.3)	45.7 (6.3)	45.8 (6.3)
Previous oral contraceptive use	543 (61.5)	561 (65.5)	545 (63.7)	541 (61.2)
Height, mean (SD), m	1.7 (0.1)	1.7 (0.1)	1.6 (0.1)	1.6 (0.1)
BMI at age 18, mean (SD), kg/m^2	19.1 (1.8)	20.2 (2.0)	21.0 (2.6)	22.6 (3.8)
Weight change since age 18, mean (SD), kg	1.1 (4.8)	5.0 (5.8)	10.0 (7.4)	22.1 (12.4)

[a]All data are expressed as number (percentage) unless otherwise specified. Data may not total 100% due to rounding.
[b]One participant with both a *BRCA1* and *BRCA2* mutation was categorized as a *BRCA1* mutation carrier.
[c]Post-menopausal women includes participants who stopped menstruation due to natural causes, had a bilateral oophorectomy with or without a hysterectomy or had radiation- or chemotherapy-induced menopause.

weight maintenance HR 0.82; 95% CI 0.49–1.39; $P=0.47$) or in the analysis stratified by menopausal status (Table 4). However, the relationship between weight change since age 18 and breast cancer risk was modified by BMI at age 18 (P-interaction $=0.01$). Among women with a BMI at age 18 of <21 kg/m^2, weight gain of 10–25 kg was associated with an increased risk of developing breast cancer compared with women who maintained their weight (HR 1.62; 95% CI 0.97–2.71; $P=0.07$). In contrast, weight change since age 18 was not associated with risk among women with a BMI at age 18 of ≥ 21 kg/m^2 (>10.0 and ≤25.0 kg weight gain vs weight maintenance HR 0.65; 95% CI 0.33–1.29; $P=0.22$). The association between weight change and breast cancer risk was not modified by *BRCA* mutation type, ER status, age at diagnosis or cause of menopause (P-interaction ≥ 0.34) (data not shown).

Height and risk of breast cancer

Height was not associated with the risk of breast cancer among all subjects in the age-adjusted or multivariable model (≥1.70 m vs ref HR 1.12; 95% CI 1.81–1.56; $P=0.50$) or in the analysis stratified by menopausal status (Table 5). After stratification by *BRCA* mutation type, there was evidence for a positive linear trend of increased breast cancer risk among *BRCA2* mutation carriers (P-trend $=0.05$), although the interaction term showed no evidence of effect modification by *BRCA* mutation type (P-interaction $=0.28$). The association between height and breast cancer risk was not modified by ER status, age at diagnosis or cause of menopause (P-interaction ≥0.39) (data not shown).

Discussion

In this first prospective evaluation of body size and breast cancer risk in *BRCA* mutation carriers, we studied 3734 female *BRCA* mutation carriers over a mean follow-up of 5.5 years. Overall, there was no observed association between height, BMI or weight change and breast cancer risk. After stratification by menopausal status, women in the highest quartile of BMI at age 18 (≥22.1 kg/m^2) had a 51% decreased risk of developing post-menopausal breast cancer compared with women with BMI at age 18 between

Table 2. BMI at age 18, current BMI and risk of breast cancer among *BRCA* mutation carriers

	Cases/total *n*	Age-adjusted HR (95% CI)	*P*-value	Cases/total *n*[a]	Multivariable HR (95% CI)[b]	*P*-value
BMI at age 18, kg/m^2						
All						
<18.8	67/812	0.85 (0.62, 1.17)	0.31	67/811	0.86 (0.62, 1.17)	0.33
18.8 to <20.3	92/898	1.00 (Ref)	Ref	92/898	1.00 (Ref)	Ref
20.3 to <22.1	80/816	0.96 (0.71, 1.30)	0.80	80/816	0.98 (0.73, 1.33)	0.91
≥22.1	64/855	0.80 (0.58, 1.09)	0.16	64/855	0.80 (0.58, 1.10)	0.16
P-trend			0.55			0.54
BRCA1						
<18.8	55/676	0.80 (0.56, 1.13)	0.20	55/675	0.81 (0.57, 1.15)	0.23
18.8 to <20.3	75/702	1.00 (Ref)	Ref	75/702	1.00 (Ref)	Ref
20.3 to <22.1	63/633	0.97 (0.69, 1.35)	0.85	63/633	0.99 (0.71, 1.38)	0.94
≥22.1	49/634	0.78 (0.54, 1.14)	0.17	49/634	0.77 (0.54, 1.11)	0.16
P-trend			0.98			0.99
BRCA2						
<18.8	12/136	1.13 (0.54, 2.37)	0.74	12/136	1.12 (0.53, 2.35)	0.76
18.8 to <20.3	17/196	1.00 (Ref)	Ref	17/196	1.00 (Ref)	Ref
20.3 to <22.1	17/183	0.96 (0.49, 1.89)	0.92	17/183	0.98 (0.50, 1.92)	0.95
≥22.1	15/221	0.88 (0.44, 1.76)	0.72	15/221	0.88 (0.44, 1.77)	0.72
P-trend			0.56			0.58
Current BMI, kg/m^2						
All						
<20.9	51/761	0.75 (0.53, 1.06)	0.10	51/761	0.75 (0.53, 1.07)	0.11
20.9 to <23.3	82/879	1.00 (Ref)	Ref	82/878	1.00 (Ref)	Ref
23.3 to <26.6	96/927	1.07 (0.80, 1.44)	0.64	96/926	1.06 (0.79, 1.43)	0.69
≥26.6	84/1009	0.84 (0.61, 1.14)	0.25	84/1009	0.81 (0.60, 1.11)	0.20
P-trend			0.91			0.75
BRCA1						
<20.9	41/632	0.71 (0.48, 1.06)	0.09	41/632	0.73 (0.49, 1.08)	0.11
20.9 to <23.3	66/706	1.00 (Ref)	Ref	66/705	1.00 (Ref)	Ref
23.3 to <26.6	80/734	1.12 (0.81, 1.56)	0.50	80/733	1.11 (0.80, 1.54)	0.54
≥26.6	68/775	0.84 (0.60, 1.19)	0.33	68/775	0.82 (0.58, 1.16)	0.27
P-trend			0.59			0.76
BRCA2						
<20.9	10/129	0.93 (0.42, 2.04)	0.85	10/129	0.89 (0.40, 1.96)	0.77
20.9 to <23.3	16/173	1.00 (Ref)	Ref	16/173	1.00 (Ref)	Ref
23.3 to <26.6	16/193	0.88 (0.44, 1.76)	0.71	16/193	0.88 (0.44, 1.76)	0.71
≥26.6	16/234	0.79 (0.39, 1.50)	0.50	16/234	0.78 (0.39, 1.56)	0.48
P-trend			0.72			0.76

[a]The multivariable model has fewer participants due to missing observations for menopausal status ($n \leq 2$).

[b]The multivariable model adjusted for age at baseline (continuous), *BRCA* mutation type (*BRCA1* or *BRCA2*), country of residence (North America, Poland or other), parity (ever or never had a live birth; time-dependent) and menopausal status (pre-menopausal or post-menopausal; time-dependent). *BRCA* mutation type was removed as a covariate from the multivariable model in the analysis stratified by *BRCA* mutation type.

18.8 and 20.3 kg/m^2. Among women with a BMI at age 18 <21 kg/m^2, weight gain of 10–25 kg was associated with an increased risk of developing breast cancer, compared with women who maintained their weight. These findings suggest that BMI in early adulthood is of importance in *BRCA*-associated breast cancer.

Few studies have evaluated body size and breast cancer risk in this high-risk population. In the largest retrospective study published to date, we previously found that weight loss of ≥10 pounds (4.5 kg) between the ages of 18 and 30 years was associated with a 53% decreased risk of breast cancer diagnosed between the ages of 30 and 40 years compared with those who maintained weight.[12] Change in body weight at ages 30–40 did not influence risk.[12] King *et al.* reported that a healthy weight early in life was associated with a delay in breast cancer diagnosis,[11] whereas another study found no association between BMI and diagnosis age among 46 *BRCA1* mutation

Table 3. BMI at age 18, current BMI and risk of breast cancer by menopausal status

	Cases/total *n*	Age-adjusted HR (95% CI)	*P*-value	Cases/total *n*	Multivariable HR (95% CI)[a]	*P*-value
BMI at age 18, kg/m^2						
Pre-menopausal						
<18.8	42/522	1.06 (0.69, 1.61)	0.80	42/522	1.06 (0.69, 1.61)	0.80
18.8 to <20.3	45/522	1.00 (Ref)	Ref	45/522	1.00 (Ref)	Ref
20.3 to <22.1	47/486	1.26 (0.84, 1.90)	0.27	47/486	1.26 (0.84, 1.90)	0.27
≥22.1	42/506	1.14 (0.75, 1.74)	0.53	42/506	1.14 (0.75, 1.73)	0.56
P-trend			0.65			0.68
Post-menopausal						
<18.8	25/289	0.66 (0.41, 1.08)	0.10	25/289	0.66 (0.41, 1.07)	0.09
18.8 to <20.3	47/376	1.00 (Ref)	Ref	47/376	1.00 (Ref)	Ref
20.3 to <22.1	33/330	0.71 (0.46, 1.11)	0.13	33/330	0.73 (0.47, 1.14)	0.16
≥22.1	22/349	0.49 (0.30, 0.82)	0.006	22/349	0.49 (0.30, 0.82)	0.006
P-trend			0.33			0.34
Current BMI, kg/m^2						
Pre-menopausal						
<20.9	35/578	0.74 (0.47, 1.14)	0.17	35/578	0.74 (0.48, 1.15)	0.18
20.9 to <23.3	47/566	1.00 (Ref)	Ref	47/566	1.00 (Ref)	Ref
23.3 to <26.6	56/517	1.37 (0.93, 2.02)	0.11	56/517	1.34 (0.91, 1.98)	0.14
≥26.6	39/462	1.00 (0.65, 1.53)	0.99	39/462	0.97 (0.63, 1.48)	0.88
P-trend			0.22			0.31
Post-menopausal						
<20.9	16/183	0.88 (0.48, 1.58)	0.66	16/183	0.87 (0.48, 1.57)	0.65
20.9 to <23.3	35/312	1.00 (Ref)	Ref	35/312	1.00 (Ref)	Ref
23.3 to <26.6	40/409	0.78 (0.50, 1.23)	0.29	40/409	0.78 (0.49, 1.22)	0.27
≥26.6	45/547	0.68 (0.43, 1.05)	0.08	45/547	0.66 (0.42, 1.03)	0.07
P-trend			0.34			0.27

[a]The multivariable model adjusted for age at baseline (continuous), *BRCA* mutation type (*BRCA1* or *BRCA2*), country of residence (North America, Poland or other) and parity (ever or never had a live birth; time-dependent).

carriers.[10] A small study of 137 French-Canadian mutation carriers reported weight gain since both ages 18 and 30 were associated with 4-fold increased risk of breast cancer.[13] In the most recent publication, Manders *et al.* reported that high vs low body weight was associated with a 2.1-fold increased risk of post-menopausal, but not pre-menopausal, breast cancer.[14] These prior reports were all retrospective and included a small number of *BRCA* mutation carriers, and most did not account for menopausal status or *BRCA* mutation type.

We observed no relationship between BMI at age 18 or current BMI and risk of breast cancer among all women; however, high BMI at age 18 decreased risk of post-menopausal breast cancer. The findings were similar in women with natural and surgical menopause, and in women diagnosed before and after age 50, suggesting menopausal status is the most relevant effect modifier for BMI at age 18 and risk. These findings are in line with the World Cancer Research Fund/American Institute for Cancer Research Continuous Update Project Report, which concluded that there is strong evidence that body fatness between ages 18 and 30 years decreases risk for post-menopausal breast cancer.[6] In a dose–response meta-analysis of 17 studies, there was an 18% decreased risk of post-menopausal breast cancer per 5 kg/m^2 (RR 0.82; 95% CI 0.76–0.88).[6]

There are several postulated mechanisms by which obesity in early adulthood may protect against post-menopausal breast cancer. First, an increased level of circulating endogenous sex hormones early in life may result in earlier differentiation of breast cells, and subsequently decrease their susceptibility to neoplastic transformation upon exposure to carcinogens.[1] Second, higher body weight at an early age is associated with lower adult levels of IGF-1 compared with those who are thinner at an early age. Lower levels of IGF-1 may confer lifetime protection against breast cancer given higher circulating levels of IGF-1 have been associated with increased cell proliferation and carcinogenesis.[2,19] Lastly, larger body weight in early life has been associated with lower mammographic density, a well-established biomarker of breast cancer risk.[2,20] It is plausible that increased body fat throughout early life could confer lifelong protection that extends into the

Table 4. Weight change since age 18 and risk of breast cancer among *BRCA* mutation carriers

	Cases/total *n*	Age-adjusted HR (95% CI)	*P*-value	Cases/total *n*[a]	Multivariable HR (95% CI)[b]	*P*-value
Weight change since age 18, kg						
All subjects						
>2.0 loss	18/300	0.77 (0.43, 1.38)	0.38	18/300	0.75 (0.42, 1.34)	0.33
2.0 loss and 2.0 gain	31/433	1.00 (Ref)	Ref	31/433	1.00 (Ref)	Ref
>2.0 and ≤10.0 gain	93/1067	1.11 (0.74, 1.67)	0.62	93/1067	1.09 (0.72, 1.63)	0.70
>10.0 and ≤25.0 gain	121/1125	1.29 (0.86, 1.93)	0.22	121/1124	1.24 (0.82, 1.86)	0.31
>25.0 gain	29/393	0.87 (0.51, 1.46)	0.59	29/393	0.82 (0.49, 1.39)	0.47
P-trend			0.76			0.90
Pre-menopausal						
>2.0 loss	15/219	0.96 (0.50, 1.85)	0.90	15/219	0.94 (0.49, 1.82)	0.87
2.0 loss and 2.0 gain	22/324	1.00 (Ref)	Ref	22/324	1.00 (Ref)	Ref
>2.0 and ≤10.0 gain	55/710	1.08 (0.66, 1.77)	0.77	55/710	1.05 (0.64, 1.73)	0.84
>10.0 and ≤25.0 gain	66/595	1.51 (0.92, 2.46)	0.10	66/595	1.43 (0.87, 2.34)	0.16
>25.0 gain	11/157	0.88 (0.42, 1.83)	0.73	11/157	0.83 (0.40, 1.73)	0.62
P-trend			0.50			0.65
Post-menopausal						
>2.0 loss	3/81	0.36 (0.10, 1.33)	0.13	3/81	0.36 (0.10, 1.32)	0.12
2.0 loss and 2.0 gain	9/109	1.00 (Ref)	Ref	9/109	1.00 (Ref)	Ref
>2.0 and ≤10.0 gain	38/357	1.08 (0.52, 2.23)	0.84	38/357	1.07 (0.52, 2.22)	0.85
>10.0 and ≤25.0 gain	55/529	0.97 (0.48, 1.97)	0.94	55/529	0.97 (0.48, 1.96)	0.93
>25.0 gain	18/236	0.75 (0.34, 1.67)	0.48	18/236	0.73 (0.33, 1.63)	0.44
P-trend			0.83			0.79
BMI at age 18 <21 kg/m^2						
>2.0 loss	5/78	0.86 (0.32, 2.32)	0.77	5/78	0.84 (0.31, 2.27)	0.73
2.0 loss and 2.0 gain	18/271	1.00 (Ref)	Ref	18/271	1.00 (Ref)	Ref
>2.0 and ≤10.0 gain	62/710	1.22 (0.72, 2.07)	0.46	62/710	1.18 (0.70, 2.00)	0.54
>10.0 and ≤25.0 gain	97/758	1.69 (1.01, 2.83)	0.04	97/757	1.62 (0.97, 2.71)	0.07
>25.0 gain	13/238	0.69 (0.33, 1.42)	0.31	13/238	0.64 (0.31, 1.34)	0.24
P-trend			0.55			0.46
BMI at age 18 ≥21 kg/m^2						
>2.0 loss	13/220	0.64 (0.30, 1.40)	0.27	13/220	0.64 (0.30, 1.38)	0.25
2.0 loss and 2.0 gain	13/161	1.00 (Ref)	Ref	13/161	1.00 (Ref)	Ref
>2.0 and ≤10.0 gain	31/351	0.96 (0.50, 1.84)	0.91	31/351	0.96 (0.50, 1.84)	0.90
>10.0 and ≤25.0 gain	24/361	0.67 (0.34, 1.33)	0.25	24/361	0.65 (0.33, 1.29)	0.22
>25.0 gain	16/154	1.08 (0.52, 2.24)	0.85	16/154	1.06 (0.51, 2.21)	0.88
P-trend			0.34			0.43

[a]The multivariable model has fewer participants due to missing observations for menopausal status ($n \leq 2$).

[b]The multivariable model adjusted for age at baseline (continuous), *BRCA* mutation type (*BRCA1* or *BRCA2*), country of residence (North America, Poland or other), parity (ever or never had a live birth; time-dependent) and menopausal status (pre-menopausal or post-menopausal; time-dependent). Menopausal status was removed as a covariate from the multivariable model in the analysis stratified by menopausal status.

post-menopausal period. Given the early age of breast cancer diagnosis among women with a *BRCA* mutation, earlier lifetime exposures may have a greater impact in preventing disease whereas current or more recent exposures may only influence the progression of already existing (pre)neoplastic lesions among high-risk women.

We did not observe any effect of weight change since age 18 on breast cancer risk. In the general population, weight gain since age 18 increases risk of hormone receptor-positive but not hormone receptor-negative breast cancers.[4,18] We found no interaction in our analysis stratified by ER status; however, given that *BRCA1* mutation carriers typically present with hormone receptor-negative breast cancers, the number of women with ER+ tumours was small. Interestingly, among women with a low BMI at age 18 (< 21 kg/m^2), weight gain of 10–25 kg since age 18 was associated with a 62% increased risk for breast cancer compared with women who maintained weight ($P = 0.07$). There was no association among women with a high BMI at age 18 (≥ 21 kg/m^2). Although this analysis was limited by the small number of women in each stratum, these findings suggest that BMI in early

Table 5. Height and risk of breast cancer among *BRCA* mutation carriers

	Cases/total *n*	Age-adjusted HR (95% CI)	*P*-value	Cases/total *n*[a]	Multivariable HR (95% CI)[b]	*P*-value
Height, m						
All subjects						
<1.61	113/1094	1.13 (0.83, 1.54)	0.44	113/1094	1.12 (0.82, 1.53)	0.47
1.61 to <1.65	63/713	1.00 (Ref)	Ref	63/713	1.00 (Ref)	Ref
1.65 to <1.70	80/982	0.91 (0.65, 1.27)	0.58	80/980	0.91 (0.66, 1.27)	0.59
≥1.70	82/929	1.11 (0.80, 1.55)	0.53	82/929	1.12 (0.81, 1.56)	0.50
P-trend			0.68			0.77
BRCA1						
<1.61	83/830	1.03 (0.73, 1.46)	0.86	83/830	1.03 (0.73, 1.46)	0.86
1.61 to <1.65	52/579	1.00 (Ref)	Ref	52/579	1.00 (Ref)	Ref
1.65 to <1.70	67/797	0.91 (0.63, 1.30)	0.60	67/795	0.92 (0.64, 1.32)	0.63
≥1.70	71/745	1.17 (0.82, 1.68)	0.38	71/745	1.19 (0.83, 1.71)	0.34
P-trend			0.60			0.54
BRCA2						
<1.61	30/264	1.53 (0.77, 3.06)	0.23	30/264	1.48 (0.74, 2.96)	0.26
1.61 to <1.65	11/134	1.00 (Ref)	Ref	11/134	1.00 (Ref)	Ref
1.65 to <1.70	13/185	0.92 (0.41, 2.05)	0.83	13/185	0.91 (0.41, 2.02)	0.81
≥1.70	11/184	0.85 (0.37, 1.96)	0.70	11/184	0.81 (0.35, 1.88)	0.63
P-trend			0.05			0.05
Pre-menopausal						
<1.61	53/560	1.08 (0.70, 1.65)	0.73	53/560	1.08 (0.70, 1.65)	0.74
1.61 to <1.65	35/402	1.00 (Ref)	Ref	35/402	1.00 (Ref)	Ref
1.65 to <1.70	51/607	0.92 (0.60, 1.42)	0.72	51/607	0.94 (0.61, 1.45)	0.78
≥1.70	49/627	0.93 (0.60, 1.44)	0.76	49/627	0.96 (0.62, 1.48)	0.84
P-trend			0.42			0.53
Post-menopausal						
<1.61	60/534	1.18 (0.75, 1.85)	0.47	60/534	1.17 (0.75, 1.84)	0.49
1.61 to <1.65	28/311	1.00 (Ref)	Ref	28/311	1.00 (Ref)	Ref
1.65 to <1.70	29/373	0.86 (0.51, 1.44)	0.56	29/373	0.86 (0.51, 1.44)	0.55
≥1.70	33/302	1.46 (0.88, 2.43)	0.14	33/302	1.44 (0.87, 2.40)	0.16
P-trend			0.78			0.83

[a]The multivariable model has fewer participants due to missing observations for menopausal status (n ≤2).

[b]The multivariable model adjusted for age at baseline (continuous), *BRCA* mutation type (*BRCA1* or *BRCA2*), country of residence (North America, Poland or other), parity (ever or never had a live birth; time-dependent) and menopausal status (pre-menopausal or post-menopausal; time-dependent). *BRCA* mutation type was removed as a covariate from the multivariable model in the analysis stratified by *BRCA* mutation type. Menopausal status was removed as a covariate from the multivariable model in the analysis stratified by menopausal status.

adulthood may play an important role in weight gain and risk of breast cancer.

The linear association between adult attained height and breast cancer risk among women in the general population has been attributed to an increase in circulating IGF levels with increasing height.[21–23] Similarly to our earlier retrospective study, we observed no relationship between height and the risk of *BRCA*-breast cancer in this analysis.[12] Only one other publication has evaluated the relationship between height and *BRCA*-breast cancer risk, which reported an increased risk of breast cancer among post-menopausal women with a height of ≥1.67 m compared with women with a height of <1.67 m; however, this study was retrospective and had a small sample size ($n = 719$).[14]

The current study had several strengths including the large number of unaffected women at the start of follow-up, making this the largest prospective report of body size and breast cancer in this high-risk population. Our biennial follow-up allowed accurate updating of both exposures and covariates, and the large sample size allowed stratified analyses by menopausal status and *BRCA* mutation type. Nevertheless, our study is not without limitations. Given the long latency period of breast cancer development, our follow-up time may not have been lengthy enough to account for the latency period of this disease. Only 88% of the incident cases were confirmed by review of pathology reports; however, previous studies have reported high sensitivity of self-reported breast

cancer.[24] We were less powered in the analysis stratified by ER status, since this information was obtained for 75% of the cases. Measurement bias on self-reported height and weight, particularly recall of weight at age 18, is another potential limitation; however, studies have demonstrated high reliability of self-reported anthropometric measures.[25–27] We did not have information on other measures of adiposity such as the waist-to-hip ratio or waist circumference, which have been shown to be more accurate measures of adiposity. In addition, there remains the possibility of residual confounding, as we did not have enough information on other potential confounders such as physical activity and socio-economic status. Lastly, the lack of linear trend limits the interpretability of our findings.

In conclusion, we observed no association between body size and breast cancer risk among all *BRCA* mutation carriers overall. However, after stratification by menopausal status, the inverse relationship between greater BMI at age 18 and post-menopausal breast cancer supports an important role of early rather than current or adulthood exposures for *BRCA*-associated breast cancer development. Although these findings stress the importance of early prevention and lifestyle modification for *BRCA* mutation carriers, the potential prevention implications for this high-risk population requires further evaluation. Future studies with longer follow-up and additional measures of adiposity are necessary to confirm these findings.

Supplementary Data

Supplementary data are available at *IJE* online.

Funding

This work was supported by the Champions of Genetics Grant from the Canadian Gene Cure Foundation in partnership with the Canadian Institutes of Health Research (CIHR) Institute of Genetics and Canadian Cancer Society Research Institute (grant number 703058); the Charles F. and Mary C. Heider Chair in Cancer Research, Creighton University to H.T.L.; the American Cancer Society Clinical Research Professorship (grant number SIOP-06–258-01-COUN to B.Y.K.); the Morris and Horowitz Families Endowed Professorship to S.L.N.; the Canada Research Chair tier I to S.A.N.; and the Cancer Care Ontario Research Chair in Population Studies and a Canadian Cancer Society Career Development Award in Prevention to J.K. The funding sources had no role in the design and conduct of the study; collection, management, analysis and interpretation of the data; preparation, review or approval of the manuscript; and decision to submit the manuscript for publication.

Acknowledgements

Additional contributions

We would like to acknowledge the study staff, students and volunteers Farah Shoukat MD, Ellen MacDougall MBT, Zoella Pasta MD, Sarah Chin, Shahana Nargis MD, Clotilde Ngwa MD, Mai Abdelhadi MD, Saiveena Penikalapati, Laavanya Somasundaram and Hannah Horvath from the Women's College Research Institute, Toronto, ON, Canada, who helped with the data collection and data entry.

Other collaborators of the Hereditary Breast Cancer Clinical Study Group

Peter Ainsworth, Louise Bordeleau, Nadine Tung, Eitan Friedman, Wendy Meschino, Carrie Snyder, Kelly Metcalfe, Ellen Warner, Barry Rosen, Rochelle Demsky, Jeffrey N. Weitzel, Karen Panabaker, Fergus Couch, Siranoush Manoukian, Barbara Pasini, Mary B. Daly, Linda Steele, Howard Saal, Taya Fallen, Marie Wood, Wendy McKinnon, Edmond Lemire, Albert E. Chudley, Kim Serfas, Christine Elser, Susan T. Vadaparampil, Ophira Ginsburg, Carey A. Cullinane, Joanne L. Blum, Theodora Ross, Caitlin Mauer, Ava Kwong, Cezary Cybulski, Jeanna McCuaig, Daniel Rayson and Claudine Isaacs.

Conflict of interest: None declared.

References

1. Baer HJ, Tworoger SS, Hankinson SE, Willett WC. Body fatness at young ages and risk of breast cancer throughout life. *Am J Epidemiol* 2010;**171**:1183–94.
2. Oh H, Boeke CE, Tamimi RM *et al.* The interaction between early-life body size and physical activity on risk of breast cancer. *Int J Cancer* 2015;**137**:571–81.
3. Palmer JR, Adams-Campbell LL, Boggs DA, Wise LA, Rosenberg L. A prospective study of body size and breast cancer in black women. *Cancer Epidemiol Biomarkers Prev* 2007;**16**:1795–802.
4. Rosner B, Eliassen AH, Toriola AT *et al.* Weight and weight changes in early adulthood and later breast cancer risk. *Int J Cancer* 2017;**140**:2003–14.
5. Xue F, Rosner B, Eliassen H, Michels KB. Body fatness throughout the life course and the incidence of premenopausal breast cancer. *Int J Epidemiol* 2016;**45**:1103–12.
6. World Cancer Research Fund/American Institute for Cancer Research. *Continuous Update Project Report: Diet, Nutrition, Physical Activity and Breast Cancer*. 2017. http://www.wcrf.org/int/research-we-fund/continuous-update-project-findings-reports/breast-cancer (10 August 2017, date last accessed).
7. Yung RL, Ligibel JA. Obesity and breast cancer: risk, outcomes, and future considerations. *Clin Adv Hematol Oncol* 2016;**14**:790–97.
8. Pike MC, Krailo MD, Henderson BE, Casagrande JT, Hoel DG. 'Hormonal' risk factors, 'breast tissue age' and the age-incidence of breast cancer. *Nature* 1983;**303**:767–70.
9. Henderson BE, Ross RK, Judd HL, Krailo MD, Pike MC. Do regular ovulatory cycles increase breast cancer risk? *Cancer* 1985;**56**:1206–08.
10. Chang-Claude J, Becher H, Eby N, Bastert G, Wahrendorf J, Hamann U. Modifying effect of reproductive risk factors on the age at onset of breast cancer for German BRCA1 mutation carriers. *J Cancer Res Clin Oncol* 1997;**123**:272–79.
11. King MC, Marks JH, Mandell JB, Group NYBCS. Breast and ovarian cancer risks due to inherited mutations in BRCA1 and BRCA2. *Science* 2003;**302**:643–46.

12. Kotsopoulos J, Olopado OI, Ghadirian P *et al*. Changes in body weight and the risk of breast cancer in BRCA1 and BRCA2 mutation carriers. *Breast Cancer Res* 2005;**7**:R833–43.
13. Nkondjock A, Robidoux A, Paredes Y, Narod SA, Ghadirian P. Diet, lifestyle and BRCA-related breast cancer risk among French-Canadians. *Breast Cancer Res Treat* 2006;**98**:285–94.
14. Manders P, Pijpe A, Hooning MJ *et al*. Body weight and risk of breast cancer in BRCA1/2 mutation carriers. *Breast Cancer Res Treat* 2011;**126**:193–202.
15. Antoniou A, Pharoah PD, Narod S *et al*. Average risks of breast and ovarian cancer associated with BRCA1 or BRCA2 mutations detected in case series unselected for family history: a combined analysis of 22 studies. *Am J Hum Genet* 2003;**72**: 1117–30.
16. Narod SA. BRCA mutations in the management of breast cancer: the state of the art. *Nat Rev Clin Oncol* 2010;**7**:702–07.
17. Michels KB, Terry KL, Eliassen AH, Hankinson SE, Willett WC. Adult weight change and incidence of premenopausal breast cancer. *Int J Cancer* 2012;**130**:902–09.
18. Eliassen AH, Colditz GA, Rosner B, Willett WC, Hankinson SE. Adult weight change and risk of postmenopausal breast cancer. *JAMA* 2006;**296**:193–201.
19. Poole EM, Tworoger SS, Hankinson SE, Schernhammer ES, Pollak MN, Baer HJ. Body size in early life and adult levels of insulin-like growth factor 1 and insulin-like growth factor binding protein 3. *Am J Epidemiol* 2011;**174**:642–51.
20. Samimi G, Colditz GA, Baer HJ, Tamimi RM. Measures of energy balance and mammographic density in the Nurses' Health Study. *Breast Cancer Res Treat* 2008;**109**:113–22.
21. Zhang B, Shu XO, Delahanty RJ *et al*. Height and breast cancer risk: evidence from prospective studies and Mendelian randomization. *J Natl Cancer Inst* 2015;**107**: djv219. doi: 10.1093/jnci/djv219.
22. Green J, Cairns BJ, Casabonne D *et al*. Height and cancer incidence in the Million Women Study: prospective cohort, and meta-analysis of prospective studies of height and total cancer risk. *Lancet Oncol* 2011;**12**:785–94.
23. Pollack MN. Insulin, insulin-like growth factors, insulin resistance, and neoplasia. *Am J Clin Nutr* 2007;**86**:s820–22.
24. Abraham L, Geller BM, Yankaskas BC *et al*. Accuracy of self-reported breast cancer among women undergoing mammography. *Breast Cancer Res Treat* 2009;**118**:583–92.
25. Casey VA, Dwyer JT, Coleman KA, Krall EA, Gardner J, Valadian I. Accuracy of recall by middle-aged participants in a longitudinal study of their body size and indices of maturation earlier in life. *Ann Hum Biol* 1991;**18**:155–66.
26. Weaver TW, Kushi LH, McGovern PG *et al*. Validation study of self-reported measures of fat distribution. *Int J Obes Relat Metab Disord* 1996;**20**:644–50.
27. Must A, Willett WC, Dietz WH. Remote recall of childhood height, weight, and body build by elderly subjects. *Am J Epidemiol* 1993;**138**:56–64.