Weight Gain and the Risk of Ovarian Cancer in *BRCA1* and *BRCA2* Mutation Carriers

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ABSTRACT

Background: Weight gain and other anthropometric measures on the risk of ovarian cancer for women with *BRCA* mutations are not known. We conducted a prospective analysis of weight change since age 18, height, body mass index (BMI) at age 18, and current BMI and the risk of developing ovarian cancer among *BRCA1* and *BRCA2* mutation carriers.

Methods: In this prospective cohort study, height, weight, and weight at age 18 were collected at study enrollment. Weight was updated biennially. Cox proportional hazards models were used to estimate the hazard ratio (HR) and 95% confidence intervals (CI) for ovarian cancer.

Results: This study followed 4,340 women prospectively. There were 121 incident cases of ovarian cancer. Weight gain of more than 20 kg since age 18 was associated with a 2-fold increased risk of ovarian cancer, compared with women who maintained a stable weight (HR, 2.00; 95% CI, 1.13–3.54; $P = 0.02$). Current BMI of 26.5 kg/m^2 or greater was associated with an increased risk of ovarian cancer in *BRCA1* mutation carriers, compared with those with a BMI less than 20.8 kg/m^2 (Q4 vs. Q1 HR, 2.13; 95% CI, 1.04–4.36; $P = 0.04$). There were no significant associations between height or BMI at age 18 and risk of ovarian cancer.

Conclusions: Adult weight gain is a risk factor for ovarian cancer in women with a *BRCA1* or *BRCA2* mutation.

Impact: These findings emphasize the importance of maintaining a healthy body weight throughout adulthood in women at high risk for ovarian cancer.

Introduction

The lifetime risks of developing ovarian cancer among women with an inherited *BRCA1* and *BRCA2* mutation are estimated to be 40% and 20%, respectively (compared with 1.7% in the general population; refs. 1, 2). Given the lack of effective screening tools, risk-reducing bilateral salpingo-oophorectomy between the ages of 35 and 40 for *BRCA1* mutation carriers and between the ages of 40 and 45 for *BRCA2* mutation carriers is the standard of care (3).

Although factors such as nulliparity, exogenous hormone therapy use, and obesity increase the risk of ovarian cancer among women in the general population, few modifiable risk factors have been clearly elucidated for ovarian cancer among *BRCA* mutation carriers (4). A large number of epidemiologic studies have examined obesity and body size as risk factors in the general population (5, 6). It has been suggested that adult-attained height and body mass index (BMI) are associated with an increased risk of developing ovarian cancer (5, 7–9). Recent evidence suggests that adiposity early in life (rather than in adulthood) may be more strongly related to risk (10–12). However, few studies have examined the relationship between weight change in early adulthood and ovarian cancer incidence (13–15).

In an earlier case–control study, we observed no significant association between various anthropometric measures (including BMI and body weight) and the risk of ovarian cancer (16). However, this was a retrospective study based on 469 pairs of women (403 *BRCA1* and 66 *BRCA2*). To our knowledge, there have been no prospective studies on this topic. Thus, we conducted a prospective analysis among *BRCA*

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mutation carriers to evaluate the relationship between weight change since early adulthood, height, BMI at age 18, and current BMI with the subsequent risk of ovarian cancer.

Materials and Methods

Study population

Detailed descriptions of the study population are reported in previous studies that include the same population (2, 17). Women who had a family history of breast and/or ovarian cancer underwent genetic testing, and those who tested positive for a deleterious *BRCA1* or *BRCA2* germline mutation were included in the study. Participants were enrolled in an international longitudinal study from one of 85 participating centers across 17 countries. All participants received genetic counseling, except some from the University of Utah and the University of California Irvine. *BRCA1/2* mutations were detected and confirmed by direct DNA sequencing. Subjects included into the study provided informed consent and the study received approval from each site's institutional ethics review board.

Data collection

As part of the longitudinal study, participants completed a self-reported baseline questionnaire at enrolment. Participants then completed a self-reported follow-up questionnaire after every 2 years until the end of the study. The baseline questionnaire requested detailed data on reproductive history such as parity, hormonal medication use such as hormone replacement therapy, select lifestyle factors, including smoking, and finally, participants reported any relevant personal or family medical information. Self-reported height (feet and inches or cm), current weight (pounds or kg), and weight at age 18 (pounds or kg) were also collected. The biennial follow-up questionnaires collected updated data on various exposures, including current weight, reproductive factors, exogenous hormone use and to update disease incidence. Questionnaires were mailed or emailed to participants, or administered over the phone.

The primary outcome of the study was defined as incident epithelial ovarian or fallopian tube cancer, which was collected from the biennial follow-up questionnaires. Occult cancers diagnosed at preventive surgery were included as incident cancers. Pathology reports and medical records were requested for all women who reported incident ovarian or fallopian tube cancer. Detailed information on tumor histology, and the primary site of origin was abstracted from pathology reports and medical record review. 70% of the ovarian or fallopian tube cancer cases were confirmed with pathology reports. Given the small number of incident fallopian tube cancers, we classified the outcome as ovarian cancer.

Assessment of anthropometric measures

Height was converted to meters (m) and weight was converted to kilograms (kg) and analyzed as a time-fixed variable at baseline. BMI at age 18 was calculated as weight at age 18 in kg divided by height in meters squared (kg/m^2) and analyzed as a time-fixed variable at baseline. Current BMI was updated for each follow-up questionnaire cycle and analyzed as a time-varying exposure. Finally, weight change since age 18 was calculated as the difference between current weight and weight at age 18 at each cycle, analyzed as a time-varying exposure.

Subjects available for analysis

A total of 17,719 *BRCA1* or *BRCA2* mutation carriers were identified. We excluded women with a diagnosis of any cancer before completion of the baseline questionnaire (n = 9,852), those with missing information (i.e., date of birth, *BRCA* mutation carrier status; n = 222), and those who had a bilateral oophorectomy before the baseline questionnaire (n = 3,041), resulting in 4,604 eligible subjects. After excluding subjects with missing data, 4,340 subjects were available for the analysis of height, 3,888 for BMI at age 18, 4,102 for current BMI, and 3,853 for weight change since age 18.

Statistical analysis

BMI at age 18 and height were determined at the time of the baseline questionnaire. Current BMI was determined at the time of each follow-up questionnaire. Missing anthropometric data in the follow-up questionnaire were carried forward from the previous cycle. Height and BMI quartiles were calculated on the basis of the distribution at baseline (mean age, 36.7 years). Weight change since age 18 was divided into five categories based on the distribution of weight loss and gain in the entire cohort. A weight loss or gain of less than 5 kg was selected as the reference group (stable weight). Height, BMI at age 18, and current BMI were also examined as continuous variables by examining height per 5 cm increase and BMI per 5 kg/m^2 increase.

Cox proportional hazards models estimated the hazard ratio (HR) and 95% confidence intervals (CI) of ovarian cancer using days of follow-up as the time variable. Women were followed from enrollment into the study and censored at the date of ovarian or fallopian tube cancer diagnosis, prophylactic oophorectomy, death or last completed follow-up questionnaire date. The age-adjusted model adjusted for age at baseline (continuous), whereas the multivariable model further adjusted for *BRCA* mutation (*BRCA1* or *BRCA2*), menopausal status (premenopausal or postmenopausal, time-varying), oral contraceptive use (ever or never, time-varying), HRT use (ever or never, time-varying), and parity (continuous). Women who tested positive for both a *BRCA1* and *BRCA2* mutation were included as *BRCA1* mutation carriers due to their higher risk of cancer (n = 10). Proportional hazards assumptions were assessed using Schoenfeld residuals. Non-linearity of continuous variables was assessed using Martingale residuals and modeling natural cubic splines at five knots. Multivariable model selection was determined on the basis of the purposeful selection of covariates as described previously by Hosmer and colleagues (18).

We *a priori* evaluated effect modification by *BRCA* mutation (*BRCA1* vs. *BRCA2*). Statistical significance of the interaction term was assessed by calculating a $P_{\text{interaction}}$ using the likelihood ratio test.

All analyses were performed using the SAS statistical package, version 9.4 (SAS Institute). All P values were two-sided and considered statistically significant if P was less than 0.05.

Results

Table 1 summarizes the baseline characteristics of 4,157 *BRCA* mutation carriers included in the analysis.

The mean height of the participants was 1.65 m (range, 1.30–2.03 m). The mean BMI at age 18 was 20.8 kg/m^2 and the mean BMI at baseline was 24.2 kg/m$^{2.}$ The mean weight change since age 18 was 8.9 kg (range loss of 45.4 kg to gain of 88.5 kg). On average, subjects with a higher BMI at baseline were older and had an earlier age at menarche compared with those with a lower BMI. In addition, subjects with a higher BMI were more likely to be parous, postmenopausal, and to have a history of HRT use, compared with those with a lower BMI at baseline.

After an average of 8.1 years of follow-up (range, 0.1–23.6), there were 121 incident epithelial ovarian or fallopian tube cancers. The

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

Characteristic	BMI at baseline (kg/m^2)			
	<20.8 (n = 1,054)	20.8–<23.1 (n = 1,052)	23.1–<26.5 (n = 1,020)	≥26.5 (n = 1,031)
Age, mean (SD), y	31.0 (10.1)	35.5 (11.2)	38.9 (11.3)	41.5 (12.5)
Mutation type[b]				
BRCA1	872 (82.8)	810 (77.5)	776 (77.2)	746 (72.8)
BRCA2	181 (17.2)	235 (22.5)	229 (22.8)	279 (27.2)
Age at menarche, mean (SD), y	13.2 (1.5)	13.2 (1.4)	13.1 (1.5)	12.8 (1.6)
Parity				
Nulliparous	512 (50.5)	370 (36.5)	268 (26.8)	234 (23.2)
1	192 (18.9)	190 (18.7)	185 (18.5)	159 (15.7)
2	204 (20.1)	291 (28.7)	327 (32.7)	372 (36.8)
≥3	106 (10.5)	163 (16.1)	221 (22.0)	246 (24.3)
Menopausal status				
Premenopausal	972 (92.5)	931 (88.7)	824 (81.0)	764 (74.1)
Postmenopausal	79 (7.5)	119 (11.3)	193 (19.0)	267 (25.9)
Previous oral contraceptive use	660 (63.1)	689 (66.3)	372 (63.1)	375 (63.3)
History of hormone replacement therapy use	31 (3.0)	58 (5.5)	71 (7.0)	91 (8.9)
Height, mean (SD), m	1.66 (0.07)	1.65 (0.07)	1.64 (0.07)	1.64 (0.07)
Weight, mean (SD), kg	53.7 (5.1)	59.8 (5.0)	66.3 (5.8)	82.9 (13.5)

[a]All data are expressed as number (percentage) unless otherwise specified. Data may not total 100% due to rounding.
[b]Participants with both a *BRCA1* and *BRCA2* mutation were categorized as a *BRCA1* mutation carrier.

histologic distribution of the 121 cancers was: 48 serous, 8 endometrioid, 29 other histology (e.g., mucinous or mixed histology), and 36 missing pathology information.

Women who gained more than 20 kgs since the age of 18 had a significant 2-fold increased risk of developing ovarian cancer compared with women whose weight remained stable (loss or gain of 5 kg; multivariable HR, 2.00; 95% CI, 1.13–3.54; P = 0.02; **Table 2**). Although not statistically significant, weight gain between 5 and 10 kg was associated with an HR of 1.51 (95% CI, 0.82–2.79; P = 0.18) and a weight gain between 10 and 20 kg was associated with an HR of 1.62 (95% CI, 0.92–2.85; P = 0.10), compared with women who had stable weight since age 18. There was no significant heterogeneity in the association between weight change and risk of ovarian cancer by *BRCA* mutation ($P_{interaction}$ = 0.78). Weight gain of 20 kg was associated with a significant increased risk among women with a *BRCA1* mutation (HR, 1.89; 95% CI, 1.04–3.44; P = 0.04) compared with those with stable weight since age 18, and although based on small strata, the data suggest a similar relationship among *BRCA2* mutation carriers (Supplementary Table S1).

There was no association between height and the risk of ovarian cancer among *BRCA* mutation carriers (**Table 3**). The multivariable HR comparing women in the highest (≥1.70 m) vs. lowest (<1.61 m) quartile of height was 1.16 (95% CI, 0.68–1.97; P = 0.59). Similarly, there was no linear association between height and the risk of ovarian cancer (P_{trend} per 5 cm increase = 0.25). The association between height and ovarian cancer risk was not significantly modified after stratification by *BRCA* mutation type ($P_{interaction}$ = 0.95). The HR for ovarian cancer risk comparing women in the highest versus lowest quartile of height was 1.14 (95% CI, 0.65–1.99; P = 0.65) for *BRCA1* mutation carriers and was 1.28 (95% CI, 0.22–7.55; P = 0.79) for *BRCA2* mutation carriers (Supplementary Table S2).

Table 4 summarizes the age-adjusted and multivariable HRs of BMI at age 18 and the risk of ovarian cancer. The multivariable HR comparing women with in the highest (≥22.2 kg/m^2) vs. lowest (<18.8 kg/m^2) quartile of BMI at age 18 was 0.93 (95% CI, 0.56–1.54; P = 0.78). There was no significant linear association between BMI at age 18 and risk of ovarian cancer (P_{trend} = 0.84). The HR comparing the highest versus lowest quartile of BMI at age 18 was 0.88 (95% CI, 0.51–1.15; P = 0.65) for *BRCA1* and 1.74 (95% CI, 0.33–9.07; P = 0.51) for *BRCA2* mutation carriers ($P_{interaction}$ = 0.83; Supplementary Table S3).

Although not statistically significant, the multivariate HR for ovarian cancer comparing women in the highest (≥26.5 kg/m^2) versus lowest (<20.8 kg/m^2) quartile of current BMI was 1.84 (95% CI, 0.95–

Table 2. Weight change and risk of ovarian cancer among *BRCA* mutation carriers.

	Cases/total n	Age-adjusted HR (95% CI)	P	Cases/total n[a]	Multivariable HR (95% CI)[b]	P
Weight change since age 18, kg						
>5.0 loss	4/162	1.34 (0.50–3.93)	0.59	4/160	1.14 (0.39–3.35)	0.82
5.0 loss and 5.0 gain	21/1,284	Ref	Ref	21/1,258	Ref	Ref
>5.0 and ≤10.0 gain	22/718	1.68 (0.92–3.06)	0.09	21/702	1.51 (0.82–2.79)	0.18
>10.0 and ≤20.0 gain	30/946	1.68 (0.96–2.97)	0.07	30/916	1.62 (0.92–2.85)	0.10
>20.0 gain	32/743	2.10 (1.19–3.72)	0.01	32/727	2.00 (1.13–3.54)	0.02
BRCA mutation interaction						0.78

[a]The multivariable model has fewer participants due to missing observations for the covariates included in the model.
[b]The multivariable model adjusted for age at baseline (continuous), *BRCA* mutation type (*BRCA1* or *BRCA2*), menopausal status (premenopausal or postmenopausal), oral contraceptive use (ever or never), HRT use (ever or never), and parity (continuous).

Table 3. Height and risk of ovarian cancer among *BRCA* mutation carriers.

	Cases/total *n*	Age-adjusted HR (95% CI)	*P*	Cases/total *n*[a]	Multivariable HR (95% CI)[b]	*P*
Height, m						
<1.61	40/1,243	Ref	Ref	39/1,196	Ref	Ref
1.61–<1.65	27/802	1.36 (0.83–2.23)	0.23	27/772	1.40 (0.84–2.32)	0.19
1.65–<1.70	28/1,159	1.01 (0.62–1.65)	0.98	28/1,115	1.09 (0.66–1.80)	0.74
≥1.70	26/1,136	1.15 (0.69–1.93)	0.59	25/1,106	1.16 (0.68–1.97)	0.59
Height, per 5 cm	121/4,340	1.05 (0.92–1.20)	0.44	119/4,189	1.08 (0.95–1.24)	0.25
BRCA mutation interaction						0.95

[a]The multivariable model has fewer participants due to missing observations for the covariates included in the model.
[b]The multivariable model adjusted for age at baseline (continuous), *BRCA* mutation type (*BRCA1* or *BRCA2*), menopausal status (premenopausal or postmenopausal), oral contraceptive use (ever or never), HRT use (ever or never), and parity (continuous).

3.56; $P = 0.07$; **Table 4**). There was no significant linear association between current BMI and risk of ovarian cancer ($P_{trend} = 0.17$). *BRCA1* mutation carriers in the highest quartile of BMI had a significant 2-fold increased risk of ovarian cancer compared with those in the lowest quartile (HR, 2.13; 95% CI, 1.04–4.36; $P = 0.04$). The corresponding HR for *BRCA2* mutation carriers was 0.70 (95% CI, 0.12–3.97; $P = 0.69$) but this was based on a small number of cases ($P_{interaction} = 0.07$; Supplementary Table S3).

Discussion

We observed that women who gained more than 20.0 kg since age 18 had a 2-fold increased risk of developing ovarian cancer compared with those with a stable body weight. Although not statistically significant, there was a suggestive increased risk of ovarian cancer among women in the highest (≥26.5 kg/m^2) versus lowest quartile of current BMI (<20.8 kg/m^2) among women with a *BRCA1* mutation. Overall, there was no significant association between height or BMI at age 18 and risk. These findings are consistent with findings from studies conducted among women at baseline population risk suggesting a harmful role of weight gain over time (10, 15). To our knowledge, this presents the first prospective analysis of body size and ovarian cancer risk specifically among women with a *BRCA1* and *BRCA2* mutation.

In an earlier retrospective case–control analysis of body size and ovarian cancer among 403 pairs of *BRCA1* and 66 pairs of *BRCA2* mutation carriers, we similarly observed no association between height, weight or BMI and ovarian cancer (16). However, the retrospective analysis found no association between changes in body weight and ovarian cancer (16). Although the studies included a similar population, the previous study was conducted in a smaller subset of participants and did not examine weight changes prospectively as a time-varying exposure; these limitations may explain the differences in our findings. We are not aware of any other published studies on the topic of body size and *BRCA*-ovarian cancer.

Few studies have assessed the association between weight change over time and risk of ovarian cancer. Aune and colleagues (14) reported no significant association between weight gain in early adulthood and ovarian cancer risk in a meta-analysis of six cohort studies. However, of the six studies, only one assessed weight change as an exposure that was updated biennially throughout follow-up (19). The other five studies assessed weight change from early adulthood to study enrollment (baseline). Examining weight change from early adulthood to study enrollment as a fixed variable is a methodologic limitation and does not use weight change as a time-varying exposure and may explain the differences between our findings. In a well-designed study with weight updated biennially from the Nurses' Health Study, authors reported an

Table 4. BMI and risk of ovarian cancer among *BRCA* mutation carriers.

	Cases/total *n*	Age-adjusted HR (95% CI)	*P*	Cases/total *n*[a]	Multivariable HR (95% CI)[b]	*P*
BMI at age 18, kg/m^2						
<18.8	30/931	Ref	Ref	30/912	Ref	Ref
18.8–<20.3	27/1,004	0.71 (0.42–1.20)	0.21	27/986	0.74 (0.44–1.25)	0.25
20.3–<22.2	21/979	0.58 (0.33–1.02)	0.06	20/956	0.59 (0.33–1.04)	0.07
≥22.2	32/974	0.92 (0.55–1.51)	0.73	32/940	0.93 (0.56–1.54)	0.78
BMI at age 18, per 5 kg/m^2	110/3,888	0.96 (0.70–1.33)	0.81	109/3,794	0.97 (0.70–1.35)	0.84
BRCA mutation interaction						0.83
Current BMI, kg/m^2						
<20.8	12/857	Ref	Ref	12/835	Ref	Ref
20.8–<23.1	27/985	1.63 (0.83–3.24)	0.16	27/958	1.55 (0.78–3.08)	0.22
23.1–<26.5	33/1,019	1.76 (0.90–3.43)	0.10	31/976	1.67 (0.85–3.28)	0.14
≥26.5	42/1,241	1.81 (0.94–3.50)	0.08	42/1,197	1.84 (0.95–3.56)	0.07
Current BMI, per 5 kg/m^2	114/4,102	1.10 (0.93–1.30)	0.28	112/3,966	1.13 (0.95–1.34)	0.17
BRCA mutation interaction						0.07

[a]The multivariable model has fewer participants due to missing observations for the covariates included in the model.
[b]The multivariable model adjusted for age at baseline (continuous), *BRCA* mutation type (*BRCA1* or *BRCA2*), menopausal status (premenopausal or postmenopausal), oral contraceptive use (ever or never), HRT use (ever or never), and parity (continuous).

increased risk of ovarian cancer with BMI change between ages 10 and 18 (HR for each 5 kg/m^2 increase = 1.24; 95% CI, 1.11–1.39) as well as since age 18 (HR for each 5 kg/m^2 increase = 1.06; 95% CI, 0.99–1.14) suggesting that early life changes may be of greater importance than weight gain in adulthood (10).

We found no association between height and risk of ovarian cancer that contradicts the findings in the general population. In a recent meta-analysis, including 24 studies and 16,062 cases, each 5 cm increment of height was associated with a significant 8% increased risk of ovarian cancer (RR, 1.08; 95% CI, 1.06–1.11; ref. 5). However, in a recent Mendelian randomization study among 22,588 *BRCA* mutation carriers enrolled in the CIMBA consortium, Qian and colleagues (20) reported no association between observed height and risk of ovarian cancer (HR, 1.07; 95% CI, 0.94–1.23) per 10 cm increase, nor between the genetically predicted height genetic score and ovarian cancer risk (HR, 1.02; 95% CI, 0.85–1.23). Therefore, our study findings may be more consistent with *BRCA*-associated ovarian cancers specifically.

Numerous analyses of body size and the risk of ovarian cancer have been conducted among women in the general population (5, 13, 21). Collectively, adiposity is associated with a weak-to-moderate increased risk of ovarian cancer (5). In the most recent World Cancer Research Fund Continuous Update Project, every 5-unit increase in BMI was associated with a 6% increase in ovarian cancer risk (RR, 1.06; 95% CI, 1.00–1.12; ref. 5). Although we did not observe significant effects of BMI on risk, it may be that BMI is not a strong risk factor for *BRCA*-associated serous ovarian cancer. This may be demonstrated in the study by Qian and colleagues (22), where BMI was associated with non-serous ovarian cancer risk (HR, 1.25; 95% CI, 1.06–1.49) but not with serous ovarian cancer (HR, 0.98; 95% CI, 0.84–1.15). Similar estimates were reported for genetically determined BMI (22). Given that the majority of the *BRCA* ovarian cancers in our study are the serous subtype (23), our findings may not be consistent with previous studies as the association between obesity and ovarian cancer is stronger for the non-serous subtypes (i.e., endometrioid, mucinous and clear cell tumors; refs. 5, 21, 22).

There are several potential mechanisms by which obesity or adult attained height may influence carcinogenesis, including the dysregulation of circulating endogenous sex hormone levels, alterations in growth factors such as IGF-1, creation of a pro-inflammatory environment, as well as the development of insulin resistance (13). The impact of obesity or weight gain on the pathogenesis of *BRCA*-associated ovarian cancer is unclear. However, it may be that weight gain is a better measure of adiposity as weight gained during adulthood mainly consists of fat mass versus lean mass (5). It has been proposed that a proportion of high-grade serous cancers originate in the fallopian tubes and spread to the ovaries and/or peritoneal cavity (24–26). Of interest, findings from a few smaller studies of *BRCA* mutation carriers that evaluated whether body size is correlated with the presence of precursor lesions. In a study of 74 women with a *BRCA* mutation, Folkins and colleagues (27), found a positive correlation between BMI and the number of cortical inclusion cysts. Primas and colleagues (28), also found that increasing BMI was correlated with presence of precursor lesions, specifically, epithelial inclusions cysts, in *BRCA* mutation carriers. In a study of 173 *BRCA* mutation carriers, the proportion of women with a non-invasive lesion [defined as of either p53 overexpression ("p53-signature") or a tubal intra-epithelial carcinoma (TIC)] was 31.2% in those with a BMI of >25 kg/m^2 and 18% among those with a BMI of <25 kg/m^2 (29).

The current study had several strengths, including the prospective design, inclusion of time-varying exposures (weight change and BMI) and the longitudinal nature of our study that allowed us to evaluate early and later adulthood adiposity as well as changes over time. Nonetheless, our study is not without limitations. The use of self-reported weight at age 18 that may have resulted in measurement error with recall bias, although several others have demonstrated the validity of self-reported body size in young and later adulthood (30, 31). Diagnosis of ovarian cancer was also self-reported; however, 70% of cases were confirmed through pathology reports. We were not sufficiently powered to conduct an analysis stratified by histologic subtype and our analyses by *BRCA* mutation were not sufficiently powered. Because the majority of the study subjects are *BRCA1* mutation carriers (>70%), these findings are mostly generalizable for *BRCA1* mutation carriers, and not *BRCA2* mutation carriers. Finally, this prospective cohort study had a follow-up rate of 85% over the average 8-year study period. Because of the small level of losses and the likelihood that any losses to follow-up were non-differential, any potential biases would reduce our estimates toward the null yielding conservative findings.

In summary, we observed an important role of adult weight gain over time, with a 2-fold increased risk among those experiencing weight gain of 20 kg since age 18. This finding highlights the importance of maintaining a healthy body weight throughout adulthood and points toward an important etiologic role of weight gain trajectory affecting ovarian risk in this high-risk population. Future studies with larger sample size to stratify findings by *BRCA* mutation type, histologic subtype, and menopausal status are warranted.

Authors' Disclosures

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Authors' Contributions

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