Body Mass Index and Breast Cancer Risk Among Pre- and Postmenopausal BRCA1/2 Mutation Carriers

Samantha K. Tengs

A thesis

submitted in partial fulfillment of the

requirements for the degree of

Master of Science

University of Washington

2019

Committee:

Elizabeth A. Kirk

Katherine M. Ueland

Program Authorized to Offer Degree:

Nutritional Sciences

University of Washington

Abstract

Body Mass Index and Breast Cancer Risk Among Pre- and Postmenopausal BRCA1/2 Mutation Carriers

Samantha K. Tengs

Chair of the Supervisory Committee:

Elizabeth A. Kirk

Department of Epidemiology

Background: BRCA1/2 mutation carriers are at increased risk for breast cancer. It is of interest whether this risk is further impacted by body size, a well-established mediator in breast cancer pathology among the general population. While obesity is a positive predictor of postmenopausal breast cancer, it tends to be inversely associated with premenopausal breast cancer. The purpose of this study was to characterize BMI and compare the risk of incident pre- and postmenopausal breast cancer among normal weight and overweight/obese BRCA1/2 mutation carriers.

Methods: BMI was characterized among 359 BRCA1/2 mutation carriers using medical and lifestyle survey data. Longitudinal data on breast cancer incidence was collected via retrospective medical record review for 49 of these carriers, followed for a mean duration of 5.3

years. Incident breast cancer risk relative to BMI was calculated and compared among pre- and postmenopausal carriers.

Results: Subjects had a mean BMI of 26.3 kg/m^2, and nearly half (46.7%) were classified as overweight or obese. Among subjects followed for incident breast cancer diagnoses, no differences were observed in total incident breast cancer risk among subjects classified as normal weight and overweight/obese. After stratification by menopausal status, no differences were found in the risk of incident postmenopausal breast cancer relative to BMI, while there was a non-significant protective effect of overweight/obesity for premenopausal breast cancer.

Conclusion: BMI was not associated with breast cancer risk among pre- or postmenopausal BRCA1/2 mutation carriers. However, nearly half of BRCA1/2 mutation carriers may be impacted by overweight or obesity, suggesting the importance of further research to inform preventative recommendations for this high-risk population.

Introduction

Among women, breast cancer is the most common non-skin cancer and the second leading cause of cancer-related death.[1] Approximately 5-10% of all breast cancer cases are hereditary, with over 50% of these attributed to mutations in the breast cancer susceptibility genes BRCA1 and BRCA2.[2] These genes are involved in DNA repair and transcriptional regulation in response to DNA damage, theorized to ultimately impact tumor suppressor activities.[3] BRCA1/2 mutation carriers are estimated to have a 45-80% lifetime risk of developing breast cancer.[3,4] Given the penetrance of these mutations, it is of extreme importance to identify and address additional breast cancer risk factors to inform preventative approaches.

One such risk factor among the general population is excess adiposity, and by extension obesity.[5,6] The World Health Organization defines overweight and obesity as a body mass index (BMI) of 25-29.9 kg/m^2 and $\geq$30 kg/m^2, respectively.[7] The association between excess adiposity and increased breast cancer risk has largely been attributed to increased levels of circulating estrogens in obese women compared to non-obese women, which can influence the expression of genes involved in regulating cellular growth, differentiation, and apoptosis.[8] The increases in estrogen levels are a consequence of greater expression of aromatase in adipose tissue, the rate-limiting enzyme of estrogen biosynthesis.[8–10] Estrogen bioavailability is further increased by the inhibition of sex hormone-binding globulin production due to hyperinsulinemia, a common characteristic of obesity-associated insulin resistance.[11] Additionally, adipose tissue expansion is associated with the release of several pro-inflammatory mediators and other biological factors, including hormones, cytokines, and adipokines.[10,12] These factors are theorized to exert direct effects on neoplastic cells,[10] influence the tumor microenvironment,[10] and upregulate estradiol.[13] For example, leptin and insulin-like growth factor 1 are theorized to promote tumor cell

proliferation, while cytokines like interleukin-6 and tumor necrosis factor alpha increase adipocyte expression of aromatase and reduce secretion of adiponectin, limiting its seemingly protective effects.[10,12,13]

The relationship between body size and breast cancer risk appears to be modified by menopausal status. Obesity tends to be a positive predictor of postmenopausal breast cancer,[14–19] yet appears to be inversely associated with premenopausal breast cancer.[15,17,18,20] These trends have been confirmed by investigators of the World Cancer Research Fund and the American Institute for Cancer Research, as reported in their 2018 update.[17] Among premenopausal women, there was strong evidence of overweight and obesity reducing breast cancer risk. There was also strong evidence that postmenopausal breast cancer risk is reduced by overweight and obesity between the ages of 18 and 30, yet increases with weight gain and overweight/obesity thereafter.[17] These differential risks relative to adiposity and menopausal status have largely been attributed to differences in circulating estrogen levels. While estrogen production and bioavailability increase with greater adipose tissue among postmenopausal women, obese premenopausal women tend to have more frequent anovulation and consequently lower levels of circulating sex steroid hormones.[8,9,21] Given that BRCA1/2 mutation carriers typically develop breast cancer between the ages of 30 and 50,[22] with nearly 80% of BRCA1-associated breast cancers diagnosed premenopausally,[3] the modifying effect of menopausal status on BRCA-associated breast cancer risk relative to body size warrants further investigation.

While body size trends among the general population have been closely tracked,[23] little is known about the BRCA1/2 mutation carrier population. To date, only two studies have reported on BMI among BRCA1/2 mutation carriers.[24,25] Furthermore, while the relationship between body size and breast cancer risk has been well-established among the general population,

whether those associations apply to BRCA1/2 mutation carriers is unknown. Some studies have correlated weight loss,[26] less weight gain,[27,28] and lower weight or BMI in early adulthood[25,29] with reduced breast cancer risk and delayed onset among BRCA1/2 mutation carriers. Conversely, other studies among BRCA1/2 mutation carriers have observed no significant differences in breast cancer risk[25,26,30] or age at diagnosis[31] relative to a variety of anthropometric measures. Given these inconsistencies, the aims of the present study were to characterize BMI and to compare pre- and postmenopausal breast cancer risk relative to BMI among a group of BRCA1 and BRCA2 mutation carriers.

Methods

Study Design

BRCA1/2 mutation carriers who presented at the Breast and Ovarian Cancer Prevention Program (BOCPP) at Seattle Cancer Care Alliance (SCCA) between 2004 and 2017 were eligible for this study. Participants were referred for cancer risk-reduction counseling through a variety of outlets, including primary care providers, oncologists, genetic counselors, SCCA clinicians, and self-referral. For inclusion, participants were required to be natally-born female, at least 18 years of age, and have a BRCA1 and/or BRCA2 mutation confirmed by genetic testing. Potential participants were excluded if the mutation was not confirmed by genetic testing, or if they were unable to read, write, or speak English.

Upon presentation to the BOCPP, participants completed an intake questionnaire to assess cancer risk factors, including gynecologic, reproductive, medical, lifestyle, and family history, as well as general symptoms and cancer-related worry. Participants were excluded if they did not complete the intake questionnaire or if pertinent sections were incomplete. Follow-up data on breast cancer-related outcomes was collected for approximately one-third of participants, limited to those presenting at the BOCPP between 2004 and 2012. Breast cancer-related outcomes for which data was collected include incident cancer diagnoses, age at diagnosis or end of study period, and prophylactic surgical procedures.

Assessment of Body Mass Index, Menopausal Status, and Breast Cancer Risk

Baseline BMI was calculated using self-reported height and weight from intake questionnaires. BMI was categorized according to the World Health Organization definitions of

underweight (<18.5 kg/m^2), normal weight (18.5-24.9 kg/m^2), overweight (25-29.9 kg/m^2), and obese (≥30 kg/m^2).[7]

Self-reported menopausal status was also assessed from intake questionnaires. For breast cancer risk analyses, menopausal status at incident breast cancer diagnosis or end of study period was extrapolated from age. Women aged 51 years and older were considered postmenopausal, based on the average age of menopause onset among women in the US.[32]

Follow-up data on breast cancer outcomes was collected via retrospective medical record review through the end of the study period in 2018 or until incident breast cancer diagnosis. Breast cancer risk was assessed by measuring incident breast cancer cases relative to person-years of follow up. Subjects who had received a prophylactic mastectomy at baseline or during follow-up were excluded from breast cancer risk analyses.

Analytic Cohort

Four hundred twenty-three eligible BRCA1/2 mutation carriers were identified for this study (Figure 1). Potential participants were excluded if height and/or weight data was missing (n = 58) or if menopausal status could not be determined from gynecologic history and/or age (n = 6), leaving 359 subjects available for BMI characterization analyses. Of these, there were 197 BRCA1 mutation carriers, 160 BRCA2 mutation carriers, and two carriers of both mutations. Two hundred fifty-eight participants were classified as premenopausal and 101 as postmenopausal, with a mean age of 40.5 (± 11.5) years.

Follow-up data was collected for 140 BRCA1/2 mutation carriers (Figure 1). Potential participants were excluded if they had received a prophylactic mastectomy at baseline (n = 9) or during follow-up (n = 45), or if data was missing for height and/or weight (n = 6), breast cancer

outcomes (n = 22), mastectomies (n = 8), and follow-up duration (n = 1). Forty-nine subjects remained available for breast cancer risk analyses. Of these, 27 were classified as premenopausal and 23 as postmenopausal at the time of breast cancer diagnosis or end of study period. The mean age at initial presentation was 40.4 ($\pm$ 11.1) years and at the end of the study period was 45.8 ($\pm$ 12.3) years, with a mean follow-up duration of 5.3 ($\pm$ 4.2) years.

Statistical Analysis

Descriptive statistics were calculated among each BMI category for all BRCA1/2 mutation carriers, including BRCA mutation variant, age, menopausal status, personal and family cancer history, parity, diabetes, exercise, alcohol use, and smoking. Comparisons were made among normal weight and underweight, overweight, and obese subjects using ANOVA with post-hoc Tukey tests. The number and proportion of subjects within each BMI category was calculated and stratified by menopausal status.

Within the follow-up group, overweight and obese subjects were combined into one overweight/obese category. No underweight subjects were included in risk analyses. Descriptive statistics were calculated for normal weight and overweight/obese subjects, including BRCA mutation variant, age, menopausal status, incident breast cancer diagnoses, personal and family cancer history, parity, exercise, and alcohol use. Characteristics of normal weight and overweight/obese subjects were compared using t-tests for continuous variables and chi-square tests for categorical variables.

Cox regression hazard models were used to compare incident breast cancer risk among normal weight and overweight/obese subjects by estimating hazard ratios (HR) and 95% confidence intervals (CI), with years of follow-up as the time variable. These analyses were also

adjusted in a multivariate model. Given the limited sample size, only the most influential potential confounders identified by stepwise selection were included; baseline alcohol use and exercise. Breast cancer risk analyses were also stratified by menopausal status at cancer diagnosis or end of study period.

Statistical analyses were performed in IBM SPSS Statistics version 25. All tests were two-sided and assumed equal variances. P values of 0.05 or less were considered statistically significant.

Results

Study Population Baseline Characteristics

A total of 359 BRCA1/2 mutation carriers were included in this study, consisting of 258 premenopausal and 101 postmenopausal women with a mean age of 40.5 $\pm$ 11.5 years (Table 1). The mean BMI of this group was 26.3 $\pm$ 6.4 kg/m^2, with 50.4% (n = 181) classified as normal weight, 2.8% (n = 10) as underweight, 25.3% (n = 91) as overweight, and 21.4% (n = 77) as obese. No significant differences in BMI were found when subjects were stratified by menopausal status. The mean BMI of premenopausal BRCA1/2 mutation carriers was 26.1 $\pm$ 6.5 kg/m^2, while that of postmenopausal carriers was 26.7 $\pm$ 6.1 kg/m^2 ($p = 0.425$).

In comparison to subjects classified as normal weight, obese subjects were an average of 4.3 years older ($p = 0.035$) (Table 1). Additionally, obese subjects reported exercising less than 50% of the time of normal weight subjects ($p < 0.001$). There were no significant differences in BRCA mutation type, menopausal status, previous cancer diagnoses, family history of breast cancer, parity, diabetes, alcohol use, and smoking status among subjects classified as underweight, overweight, and obese compared to those of normal weight.

Characteristics of the Follow-Up Group

A portion of the BRCA1/2 mutation carriers (n = 49) was followed for a mean of 5.3 $\pm$ 4.2 years. During this period, there were 11 incident breast cancer diagnoses, including 5 premenopausal and 6 postmenopausal cases (Table 2). Additionally, 7 women who were premenopausal at baseline underwent menopause.

Average BMI of the follow-up group at baseline was 26.1 $\pm$ 7.3 kg/m^2. Categorically, 63.3% (n = 31) were classified as normal weight, and 36.7% (n = 18) as overweight or obese

(Table 2). No significant differences in BMI were observed among subjects in the follow-up group at baseline or follow-up when stratified by menopausal status. At baseline, premenopausal subjects had a mean BMI of 25.3 $\pm$ 7.3 kg/m^2, while postmenopausal subjects had a mean BMI of 27.7 $\pm$ 7.3 kg/m^2 (p = 0.289). At follow-up, the mean BMI of premenopausal and postmenopausal subjects was 24.7 $\pm$ 7.7 kg/m^2 and 27.6 $\pm$ 6.7 kg/m^2, respectively (p = 0.184).

In comparison to subjects classified as normal weight, overweight and obese subjects in the follow-up group were an average of over 8 years older at baseline (p = 0.007) and follow-up (p = 0.023) (Table 2). Overweight and obese subjects were also more likely to be postmenopausal at baseline (p = 0.048) and follow-up (p = 0.007) than those of normal weight. Additionally, overweight and obese subjects were more likely to be parous than subjects of normal weight (p = 0.020). No significant differences were found in BRCA mutation type, personal and family cancer history, and baseline exercise and alcohol use between subjects classified as normal weight and overweight/obese. Notably, no subjects in the follow-up group had diabetes at baseline and only 1 identified as smoker.

Risk of Incident Breast Cancer Relative to BMI and Menopausal Status in Follow-up Group

No significant differences in the risk of incident breast cancer were observed between follow-up subjects classified as normal weight and overweight/obese in unadjusted analyses (HR = 1.06; 95% CI 0.94 - 1.91; p = 0.33) (Table 3). Similarly, there were no differences in incident breast cancer risk relative to BMI category in multivariate analyses adjusted for baseline exercise and alcohol use (HR = 0.49; 95% CI 0.11 - 2.08; p = 0.33).

When stratified by menopausal status, there were no differences in the risk of incident breast cancer among overweight/obese and normal weight subjects for premenopausal (HR =

0.20; 95% CI 0.03 – 1.44; p = 0.11) and postmenopausal (HR = 1.77; 95% CI = 0.29 – 10.74; p = 0.54) breast cancer in unadjusted analyses. In multivariate analyses, no differences in the risk of postmenopausal breast cancer were observed relative to BMI classification (HR = 1.15; 95% CI = 0.15-8.71; p = 0.90). A trend toward a protective effect of overweight/obesity on the risk of premenopausal breast cancer was observed in multivariate analyses, however this finding was not statistically significant (HR = 0.10; 95% CI = 0.01 - 1.07; p = 0.06).

Discussion

The purpose of this study was to characterize BMI and compare the risk of incident pre- and postmenopausal breast cancer among normal weight and overweight/obese BRCA1/2 mutation carriers. Upon BMI characterization of 359 subjects, nearly half were classified as overweight or obese. Data on incident breast cancer diagnoses was collected for 49 of these subjects, followed for an average of 5.3 $\pm$ 4.2 years. Among this group, no differences were observed in total incident breast cancer risk among subjects classified as normal weight and overweight/obese. After stratification by menopausal status, no differences were found in the risk of incident postmenopausal breast cancer relative to BMI classification, while there was a non-significant protective effect of overweight/obesity for premenopausal breast cancer.

Only two previous studies have reported on BMI of BRCA mutation carriers. Among a group of 241 young BRCA1/2 mutation carriers, van Erkelens et al. reported a median BMI of 23.9 kg/m^2 and 41% of carriers with a BMI $\geq$ 25 kg/m^2.[24] Although the median BMI was 2.2 kg/m^2 lower than the mean BMI of premenopausal carriers in our study, the proportion of carriers classified as overweight/obese was similar. In a large prospective study of breast cancer risk relative to a variety of anthropometric measures, Kim et al. reported BMI by quartiles for 3576 BRCA1/2 mutation carriers.[25] The carriers sampled in the Kim et al. study tended to have lower BMIs than those in our study, with only 28% in the highest quartile of $\geq$ 26.6 kg/m^2, compared with 46.7% in our study population with a BMI $\geq$ 25 kg/m^2. However, similar to our findings, premenopausal carriers tended to have a lower BMI and postmenopausal carriers tended to have a higher BMI.

While several studies have evaluated breast cancer risk relative to body size among BRCA1/2 mutation carriers, only two have included BMI as a predictor.[25,28] In the

aforementioned study by Kim et al., the authors found no significant differences in breast cancer risk relative to current BMI among 3734 BRCA1/2 mutation carriers.[25] Similarly, a retrospective study by Manders et al. among 719 BRCA1/2 mutation carriers reported no impact of current BMI on breast cancer risk.[28] Although our study used baseline rather than current BMI, these findings are consistent with our results that BMI does not appear to be associated with breast cancer incidence among BRCA1/2 mutation carriers.

Other studies among BRCA1/2 mutation carriers investigating the impact of body size on breast cancer risk have reported significant findings when measuring weight or BMI at multiple time points. In a case-control study among 1073 matched pairs of BRCA1/2 mutation carriers, Kotsopoulos et al. reported that weight loss of at least 10 pounds between age 18 and 30 was associated with a reduced risk of breast cancer diagnosis between age 30 and 40.[26] However, there were no significant findings for weight gain over the same period or later weight change between the ages of 30 and 40. In another case-control study among 137 BRCA1/2 mutation carriers, Nkondjock et al. reported that reaching maximum BMI at a later age rather than in early adulthood as well as greater weight gain since ages 18 and 30 was associated with an increased risk of breast cancer.[27] Similarly, Manders et al. also observed a significant association between greater adult weight gain and higher postmenopausal breast cancer risk.[30] Finally, Kim et al. observed a significant inverse association between BMI at age 18 and postmenopausal breast cancer risk among BRCA1/2 mutation carreirs.[25] In total, these findings suggest the importance of weight or BMI at different stages of adulthood. Given this, it is possible that the inclusion of a single BMI measurement in our study was insufficient to produce meaningful results.

There were several strengths to our study. BMI characterization was based on a relatively large sample size and accounted for menopausal status. Additionally, about one-third of subjects

were followed for breast cancer outcomes over a relatively long period of time, assessed by medical record review rather than self-report. Our analyses were also stratified by menopausal status to explore any effects of this well-established breast cancer risk modifier.

However, there were also several limitations. The sample size of the follow-up group may have been too small to produce well-powered results. Additionally, the use of self-reported height and weight could have resulted in measurement bias. Finally, the use of BMI measured at only a single time point may not have been the most appropriate measure of body size. Specifically, BMI is not an accurate proxy for adiposity or its associated elevations in estrogen production, as BMI does not account for quantity, type, or distribution of body fat.[8,11] Given that BMI cannot distinguish metabolically-active visceral obesity,[11] associations between obesity defined by BMI and breast cancer risk may be biased toward the null.[33] Instead, measures like waist circumference or waist-to-hip ratio may be more appropriate in assessing breast cancer risk, as these are better indicators of visceral adiposity.[33]

In conclusion, BMI was not associated with breast cancer risk among pre- or postmenopausal BRCA1/2 mutation carriers. However, it appears that a substantial number of BRCA1/2 mutation carriers are impacted by overweight and obesity, suggesting the importance of further elucidating any possible relationship between body size and breast cancer risk among this population. Future prospective studies employing more accurate measures of body size relative to adiposity and how these measures change over time are needed to further inform preventative recommendations for BRCA1/2 mutation carriers at high-risk for breast cancer.

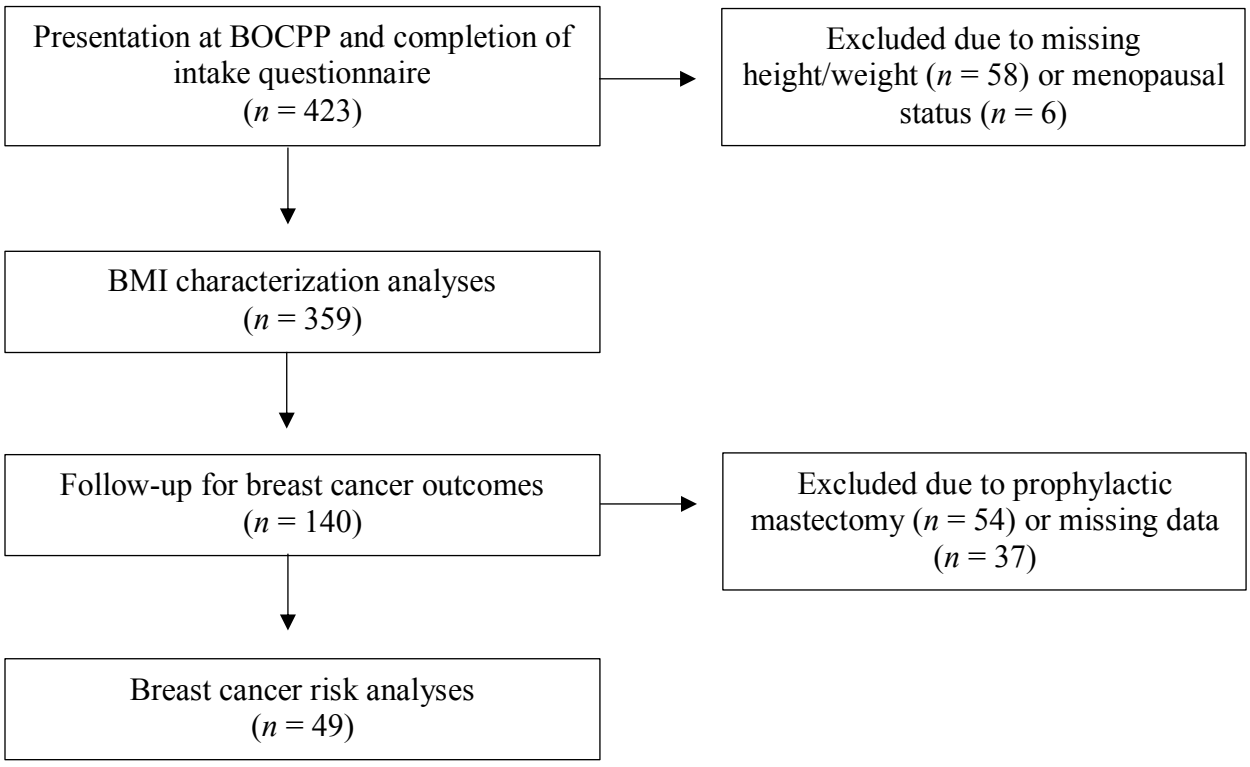

Figure 1. Flow chart of participant selection.

Table 1. Baseline characteristics of all BRCA1/2 mutation carriers by BMI classification.[a]

			BMI classification[b]			
		All[c] (n = 359)	Normal weight (n = 181)	Underweight (n = 10)	Overweight (n = 91)	Obese (n = 77)
BRCA mutation	BRCA1	197 (54.9%)	97	9	47	44
	BRCA2	160 (44.6%)	82	1	44	33
	BRCA1 and 2	2 (0.6%)	2	-	-	-
Age, years		40.5 $\pm$ 11.5	39.1	34.5	41.7	43.4 *
Menopausal status	Premenopausal	258 (71.9%)	135	8	62	53
	Postmenopausal	101 (28.1%)	46	2	29	24
Personal history of cancer	Breast	73 (14.5%)	38	-	18	17
	Non-breast	50 (13.9%)	27	1	12	10
	None	223 (64.5%)	109	8	59	47
Family history of breast cancer	Yes	301 (90.1%)	149	10	77	65
	No	33 (9.9%)	17	-	8	8
Parity	Parous	221 (62.8%)	103	8	57	53
	Nulliparous	131 (37.2%)	73	2	34	22
Diabetes diagnosis	Yes	13 (3.8%)	5	-	4	4
	No	328 (96.2%)	165	9	82	72
Exercise, hours/week		3.5 $\pm$ 3.2	4.2	3.9	3.3	2.0 **
Alcohol use	Yes	254 (71.1%)	131	7	68	48
	No	103 (28.9%)	50	3	22	28
Smoker	Yes	13 (3.7%)	5	1	1	6
	No	341 (96.3%)	174	9	89	69

a. Categorical variables are expressed as counts, while continuous variables are expressed as means. Counts for some variables may not total to the specified sample size due to missing responses.

b. BMI was categorized according to WHO definitions of underweight (<18.5 kg/m^2), normal weight (18.5-24.9 kg/m^2), overweight (25-29.9 kg/m^2), and obese ($\geq$30 kg/m^2).

c. Refers to all BRCA1/2 mutation carriers included in the study. Categorical variables are expressed as count (percentage) of total subjects. Continuous variables are expressed as mean $\pm$ standard deviation. Percentages may not total to 100% due to rounding and missing survey responses for some variables.

Significant differences relative to normal weight reference category are indicated by * for $p < 0.05$ and ** for $p < 0.005$.

Table 2. Characteristics of Follow-up Group (followed for breast cancer outcomes for an average of 5.3 years.[a, b])

			BMI classification[c]	
		All[d] (n = 49)	Normal weight (n = 31)	Overweight/obese (n = 18)
BRCA mutation	BRCA1	31 (63.3%)	19	12
	BRCA2	18 (36.7%)	12	6
Age, years	Baseline	40.4 ± 11.1	37.2	45.9 *
	Follow-up	45.8 ± 12.3	42.8	51.0 *
Menopausal status	Premenopausal, baseline	33 (67.3%)	24	9 *
	Postmenopausal, baseline	16 (32.7%)	7	9
	Premenopausal, follow-up	26 (53.1%)	21	5 *
	Postmenopausal, follow-up	23 (46.9%)	10	13
Incident breast cancer diagnosis at follow-up	Premenopausal	5 (10.2%)	3	2
	Postmenopausal	6 (12.4%)	3	3
Personal cancer history	Breast	8 (17.0%)	5	3
	Non-breast	10 (21.3%)	5	5
	None	29 (61.7%)	20	9
Family history of breast cancer	Yes	39 (90.7%)	26	13
	No	4 (9.3%)	3	1
Parity	Parous	27 (56.3%)	13	14 *
	Nulliparous	21 (43.8%)	17	4
Exercise, hours/week		4.0 ± 5.5	5.1	1.9
Alcohol use	Yes	38 (77.6%)	23	15
	No	11 (22.4%)	8	3

a. Categorical variables are expressed as counts, while continuous variables are expressed as means. Counts for some variables may not total to the specified sample size due to missing responses.

b. Variables were assessed at baseline, unless otherwise specified.

c. BMI categories were based on WHO definitions of normal weight (18.5-24.9 kg/m^2), overweight (25-29.9 kg/m^2), and obese ($\geq$30 kg/m^2).

d. Refers to all BRCA1/2 mutation carriers included in the follow-up study. Categorical variables are expressed as count (percentage) of total subjects. Continuous variables are expressed as mean ± standard deviation. Percentages may not total to 100% due to rounding and missing survey responses for some variables.

Significant differences relative to normal weight reference category are indicated by * for $p < 0.05$.

Table 3. Risk of incident breast cancer relative to BMI classification and menopausal status among BRCA1/2 mutation carriers followed for an average of 5.3 years.

	BMI classification[a]	Incident cases/total	Person-years of follow-up	Univariate HR (95% CI)	P-value	Multivariate HR (95% CI)[b]	P-value
All	Normal weight	6/31	168.1	Ref		Ref	
(n = 49)	Overweight/obese	5/18	92.4	1.06 (0.29 - 3.82)	0.93	0.49 (0.11 - 2.08)	0.33
Premenopausal	Normal weight	3/21	90.5	Ref		Ref	
(n = 26)	Overweight/obese	2/5	11.7	0.20 (0.03 - 1.44)	0.11	0.10 (0.01 - 1.07)	0.06
Postmenopausal	Normal weight	3/10	77.6	Ref		Ref	
(n = 23)	Overweight/obese	3/13	80.7	1.77 (0.29 - 10.74)	0.54	1.15 (0.15 - 8.71)	0.90

a. BMI was categorized according to WHO definitions of normal weight (18.5-24.9 kg/m^2), overweight (25-29.9 kg/m^2), and obese ($\geq$30 kg/m^2).

b. Multivariate model included average weekly exercise and alcohol use at baseline assessment as covariates.

References

1. American Cancer Society. How common is breast cancer? Current year estimates for breast cancer. https://www.cancer.org/cancer/breast-cancer/about/how-common-is-breast-cancer.html. Published 2019. Accessed April 6, 2019.
2. Bayraktar S, Amendola L, Gutierrez-Barrera AM, et al. Clinicopathologic characteristics of breast cancer in BRCA-carriers and non-carriers in women 35 years of age or less. *Breast*. 2014;23(6):770-774. doi:10.1016/j.breast.2014.08.010
3. Paul A, Paul S. The breast cancer susceptibility genes (BRCA) in breast and ovarian cancers. *Front Biosci (Landmark Ed)*. 2015;19:605-618.
4. Kobayashi H, Ohno S, Sasaki Y, Matsuura M. Hereditary breast and ovarian cancer susceptibility genes (Review). *Oncol Rep*. 2013;30(3):1019-1029. doi:10.3892/or.2013.2541
5. Kushi L, Doyle C, McCullough M, et al. American Cancer Society guidelines on nutrition and physical activity for cancer prevention. *CA Cancer J Clin*. 2012;62:30-67. doi:10.3322/caac.20140.
6. American Institute for Cancer Research. Cancer prevention recommendations. http://www.aicr.org/reduce-your-cancer-risk/recommendations-for-cancer-prevention/. Published 2018. Accessed January 10, 2019.
7. World Health Organization. Body mass index - BMI. http://www.euro.who.int/en/health-topics/disease-prevention/nutrition/a-healthy-lifestyle/body-mass-index-bmi. Published 2019. Accessed April 6, 2019.
8. Bhardwaj P, Au CC, Benito-Martin A, Ladumor H. Mechanisms involved in obesity-related development, growth and progression. *J Steroid Biochem Mol Biol*. 2019;189:161-

170. doi:10.1016/j.jsbmb.2019.03.002

9. Picon-Ruiz M, Morata-Tarifa C, Valle-Goffin JJ, Friedman ER, Slingerland JM. Obesity and adverse breast cancer risk and outcome: mechanistic insights and strategies for intervention. *CA Cancer J Clin*. 2017;67:378-397.

10. Andò S, Gelsomino L, Panza S, et al. Obesity, leptin and breast cancer: Epidemiological evidence and proposed mechanisms. *Cancers (Basel)*. 2019;11:62-89. doi:doi:10.3390/cancers11010062

11. Pischon T, Nothlings U, Boeing H. Obesity and cancer. *Proc Nutr Soc*. 2008;67:128–145. doi:10.1017/S0029665108006976

12. Choi J, Jin Cha Y, Seung Koo J. Progress in lipid research adipocyte biology in breast cancer: From silent bystander to active facilitator. *Prog Lipid Res*. 2018;69:11-20. doi:10.1016/j.plipres.2017.11.002

13. Garcia-Estevez L, Moreno-Bueno G. Updating the role of obesity and cholesterol in breast cancer. *Breast Cancer Res*. 2019;21:1-8.

14. Xia X, Chen W, Li J, et al. Body mass index and risk of breast cancer: A nonlinear dose-response meta-analysis of prospective studies. *Sci Rep*. 2014;4:7480-7484. doi:10.1038/srep07480

15. Cheraghi Z, Poorolajal J, Hashem T, Esmailnasab N, Doosti Irani A. Effect of body mass index on breast cancer during premenopausal and postmenopausal periods: a meta-analysis. *PLoS One*. 2012;7(12):1-9. doi:10.1371/journal.pone.0051446

16. White KK, Park SY, Kolonel LN, Henderson BE, Wilkens LR. Body size and breast cancer risk: The Multiethnic Cohort. *Int J Cancer*. 2012;131(5):17-20. doi:10.1002/ijc.27373

17. World Cancer Research Fund, American Institute for Cancer Research. Diet, nutrition, physical activity and breast cancer. https://www.aicr.org/continuous-update-project/reports/breast-cancer-report-2017.pdf. Published 2018. Accessed January 10, 2019.

18. Renehan AG, Tyson M, Egger M, Heller RF, Zwahlen M. Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. *Lancet*. 2008;371:569-578.

19. Neuhouser M, Argaki A, Prentice R, et al. Overweight, obesity and postmenopausal invase breast cancer risk. *JAMA Oncol*. 2015;1(5):611-621. doi:10.1001/jamaoncol.2015.1546

20. Amadou A, Ferrari P, Muwonge R, et al. Overweight, obesity and risk of premenopausal breast cancer according to ethnicity: A systematic review and dose-response meta-analysis. *Obes Rev*. 2013;14(8):665-678. doi:10.1111/obr.12028

21. La Vecchia C, Giordano SH, Hortobagyi GN, Chabner B. Overweight, obesity, diabetes, and risk of breast cancer: Interlocking pieces of the puzzle. *Oncologist*. 2011;16(6):726-729. doi:10.1634/theoncologist.2011-0050

22. Pettapiece-Phillips R, Narod SA, Kotsopoulos J. The role of body size and physical activity on the risk of breast cancer in BRCA mutation carriers. *Cancer Causes Control*. 2015;26:333–344. doi:10.1007/s10552-014-0521-0

23. Centers for Disease Control and Prevention. Overweight & Obesity, 2018. https://www.cdc.gov/ obesity/index.html. Published 2018. Accessed January 10, 2019.

24. van Erkelens A, Derks L, Sie AS, et al. Lifestyle risk factors for breast cancer in BRCA1/2-mutation carriers around childbearing age. *J Genet Couns*. 2017;26(4):785-791.

doi:10.1007/s10897-016-0049-4

25. Kim SJ, Huzarski T, Gronwald J, et al. Prospective evaluation of body size and breast cancer risk among BRCA1 and BRCA2 mutation carriers. *Int J Epidemiol*. 2018;47(3):987-997. doi:10.1093/ije/dyy039

26. 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(5):R833-R843. doi:10.1186/bcr1293

27. 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(3):285-294. doi:10.1007/s10549-006-9161-8

28. 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(1):193-202. doi:10.1007/s10549-010-1120-8

29. King MC, Marks JH, Mandell JB. Breast and ovarian cancer risks due to inherited mutations in BRCA1 and BRCA2. *Science*. 2003;302:643–646. doi:10.1126/science.1088759

30. 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. doi:10.1007/s10549-010-1120-8

31. 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(5):272–279.

32. Takahashi TA, Johnson KM. Menopause. *Med Clin N Am*. 2019;99:521-534.

doi:10.1016/j.mcna.2015.01.006

33. Avgerinos KI, Spyrou N, Mantzoros CS, Dalamaga M. Obesity and cancer risk: emerging biological mechanisms and perspectives. *Metabolism*. 2019;92:121-135. doi:10.1016/j.metabol.2018.11.001