Effect of Genetic and Lifestyle Risk Factors on the Association Between Body Mass Index and Personal History of Breast and Ovarian Cancer in the Bright Pink Population

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Abstract

Objective: To investigate the effect modification by genetic and potential lifestyle risk factors on the association between BMI and breast and ovarian cancers diagnosed among women 20-40 years of age.

Methods: We conducted a case-control analysis with 1511 breast cancer cases and 6044 controls and 1267 ovarian cancer cases and 5068 controls between 20-40 years of age. The study population and data were obtained from the Bright Pink, a national non-profit organization dedicated to the prevention and early detection of breast and ovarian cancer in young women. Cases and controls were frequency matched by age category. The association between BMI and Breast and ovarian cancers were modelled separately using logistic regression. Effect modification by hereditary gene mutations and behavioral factors including physical activity, cigarette smoking, alcohol consumption and oral contraceptive use were evaluated in each of the final models at the 0.10 significance level.

Results: Compared to the normal weight group, the underweight group had more breast cancer diagnoses ($OR_{adjusted}$ 95% CI=1.31 [1.05, 1.64]) while the obese group had less ($OR_{adjusted}$ 95% CI=0.82 [0.70, 0.96]). Only women the underweight group were significantly more likely to have a personal history of ovarian cancer compared to the normal weight group ($OR_{adjusted}$ 95% CI=1.69 [1.32, 2.15]). Physical activity, alcohol consumption, and smoking were found to be effect modifiers in the associations between BMI and breast and ovarian cancers. Being underweight was related to increased personal history of breast and ovarian cancers among women who exercised regularly, were current smokers, or had >1 drink per day while the magnitude of association was attenuated among women who did not engage in these health behaviors.

Discussion: Our study supports recent findings of BMI as a protective factor for premenopausal breast cancer in literature. Interaction between BMI and several behavioral factors suggest young, underweight women may have higher susceptibility to carcinogenic effects of environmental exposures in breast and ovarian cancer development. The results of this case-control analysis are subject to potential recall bias and reverse causality. Future prospective studies are needed to verify these findings.

Introduction

It is estimated that 12.4% or 1 in 8 women in the United States will be diagnosed with breast cancer at some point in their lifetime.[1] The lifetime risk for breast cancer can increase up to 87% for women who carry certain genetic mutations, including *BRCA1* and *BRCA2*.[2] According to the World Health Organization (WHO), breast cancer remains the most common non-melanoma cancer among women in both developed and developing nations.[3] In comparison, only 1.3% or 1 in 70 women will develop ovarian cancer in her lifetime.[1] However, public health action is still necessary as the prognosis for ovarian cancer is substantially worse with an estimated 5-year survival of 47%, compared to 88% for breast cancer.[1] For *BRCA1* carriers, the lifetime risk of developing the disease can also increase up to 63%.[2] Healthcare costs associated with breast and ovarian cancers are also significant economic burdens in the U.S., with an estimated $39 billion and $612 million spent on breast and ovarian cancer treatment each year, respectively.[4,5] Given the health and economic burdens of breast and ovarian cancers, the study of their modifiable risk factors and prevention are of great public health importance. Some well-established lifestyle risk factors for breast cancer include smoking, excess alcohol consumption, and physical inactivity, while aging and use of certain types of post-menopausal hormone therapy are associated with increased risk for both breast and ovarian cancers.[6,7]

One area of research that warrants further investigation is the association between higher body mass index (BMI) and reduced breast cancer risk in premenopausal women - where the opposite relationship is reported among post-menopausal women.[8-11] While evidence continues to support the protective effects of higher BMI against premenopausal breast cancer,

the underlying biological mechanisms remains poorly understood. The relationship between BMI and ovarian cancer is more controversial, with similar numbers of studies reporting no change in risk and increased risk with higher BMI among premenopausal women.[12,13] The current findings raise important questions regarding the biological mechanisms behind the observed negative association between BMI and breast cancer risk among premenopausal women, and what it means for future clinical practice guidelines. Additionally, most studies of the association between BMI and breast and ovarian cancers to date are conducted among women at average risk or without taking into account/measuring genetic mutation status.[8-13] Other studies have only examined the effect of BMI and breast cancer among *BRCA1/BRCA2* carriers.[14-17] This suggests that the association between BMI and breast and ovarian cancers in women at elevated risk, diagnosed with hereditary gene mutations are yet to be established.

One way to gain insight into the underlying pathophysiology between BMI and breast and ovarian cancer is to examine the effect of specific genetic and behavioral risk factors on the association. A number of hereditary genetic mutations have been linked to elevated risk of breast and/or ovarian cancers, each influencing similar but unique mechanisms in tumor onset and progression.[18-21] Assessing the relationship between BMI and individual genetic mutations can help provide insight to the biological mechanism underlying the association between BMI and breast and ovarian cancer, which can inform future treatment or prevention plans. In addition, understanding the association between BMI and breast and ovarian cancers among women with hereditary genetic mutations can also help clinicians make evidence-based risk management plans for patients at elevated risk for these morbidities. Although genetic risk factors for breast ovarian cancers are important, they are also non-modifiable. Additionally,

only 5-10% of breast cancers are thought to be hereditary, suggesting that majority of cases are sporadic in nature.[22] It is therefore also important to examine how lifestyle risk factors that may modify the association between BMI and breast and ovarian cancers to help individuals make appropriate lifestyle adjustments.

The American Cancer Society identified alcohol consumption, physical inactivity, and oral contraceptive use as behavioral factors linked to increased risk of breast cancer.[23] This declaration is supported by various systematic reviews and meta-analyses of lifestyle factors and breast cancer risk in literature.[24-27] In recent years, studies have also shown fairly consistent evidence that tobacco smoking is linked to increased risk of breast cancer.[28, 29] However, it remains inconclusive how some of these established behavioral risk factors for breast cancer interact with BMI, a relatively novel protective factor for premenopausal breast cancer, among women 20-40 years of age.[30-34] While two cohort studies reported that the adverse effects of alcohol on breast cancer risk was more prominent among women with low BMI (<25 kg/m^2, <22.5kg/m^2),[30-31] another found no significant interaction between alcohol intake and BMI.[32] In the Women's Health Initiative Observational Study, Luo et al. found that the effect of smoking on breast cancer risk was significantly modified by obesity status among post-menopausal women, where a significant association between smoking and breast cancer was observed among non-obese women only (HR=1.25, 95% CI 1.05, 1.47).[33] There exists limited evidence whether the same interaction exists among pre-menopausal women. Therefore, the effect of common modifiable risk factors on the association between BMI and breast cancer require further examination.

The relationship between lifestyle factors and ovarian cancer are less clear than breast cancer. Studies have reported inconsistent results on whether physical inactivity, fertility drug use, or tobacco smoking, or alcohol consumption is linked to higher risk of ovarian cancer.[35-38] The protective effects of breast feeding and oral contraceptive use in ovarian cancer risk reduction are more conclusive in comparison.[35, 39-41] There has also been evidence pointing to interaction among several behavioral ovarian cancer risk factors. While a number of studies have reported that there is no significant association between alcohol consumption and the development of ovarian cancer, a subgroup analysis within the meta-analysis of prospective studies conducted by Huang et al. also revealed that overall alcohol consumption was associated with increased ovarian cancer risk if not adjusted for smoking and moderate alcohol consumption was associated with increased ovarian cancer risk if not adjusted for BMI and smoking.[42-44] These findings suggest a number of these possible lifestyle risk factors for ovarian cancer may be interrelated and their potential interactions should be investigated to reach more conclusive results.

The objective of the study was to investigate the effect modification by genetic and potential lifestyle risk factors on the association between BMI and personal history of breast and ovarian cancer diagnoses among women 20-40 years of age. Based on the results from past studies, it was anticipated that BMI will be inversely associated with personal history of breast cancer only and the relationship between BMI and breast and ovarian cancers would be significantly modified by several genetic and/or behavioral factors.

Methods

We conducted a case-control analysis to examine the association between BMI and personal history of breast and ovarian cancer and whether these associations varied among women diagnosed with hereditary breast or ovarian cancer-linked gene mutations or engage in specific health behaviors. The study was approved by the Northwestern University human subjects protection program.

Cases and controls were sampled from Bright Pink's "Assess Your Risk" population. Bright Pink is a national non-profit organization dedicated to the prevention and early detection of breast and ovarian cancer in young women.[45] Through an online tool called "Assess Your Risk" (AYR) on the organization's website, women are able to assess their lifetime risk of developing breast and/or ovarian cancer based on demographics, past medical history, family history, lifestyle factors, and diagnosed hereditary breast and ovarian cancer syndromes.[46] All variables of interest used in the analysis were based on participant self-reporting during AYR completion. All questions on the AYR were multiple choice in nature.

The initial dataset contained 639,823 AYR responses collected between January 2015 – August 2018. The criteria for selecting cases included 1) self-reported personal history of breast and/or ovarian cancer on the AYR, 2) completion of the entire AYR from an IP address in the United States, 3) between 20-40 years of age at the time of completion. Participants with missing responses for any of the variables of interest in the study were excluded. All cases who met these criteria were included in the study population. Controls were randomly sampled among individuals without self-reported personal history of breast or ovarian cancer using the same criteria as cases and frequency matched to cases by age category - a known risk factor for

both breast and ovarian cancers.[6,7] Using the proc surveyselect function in SAS, we randomly sampled approximately four times as many controls as cases in each age category: 20-30, 31-35, 36-40. Frequency matching was chosen over individual matching to preserve the effective sample size during analysis. Past reports on the case-control study design have suggested that there is little benefit to the statistical power of the study beyond four controls to a case.[47]

The two primary outcomes of interest, personal history of breast cancer and personal history of ovarian cancer, were dichotomous (yes/no) and determined based on self-report during AYR completion. BMI was collected as height in imperial units and weight in pounds and converted into the following categories: Underweight <18.5, Normal Weight 18.5-24.9, Overweight 25-29.9, and Obese 30+ (kg/m^2).

Health behaviors assessed for potential confounding and effect modification in the analysis include exercise, oral contraceptive use, alcohol consumption, and smoking status. Exercise was defined as engaging in physical activity for at least 30 minutes five times a week, on average. Oral contraceptive use was defined as having taken or planning to take birth control pills for five or more years between 20-30 years of age (can be non-consecutive). Alcohol consumption was collected as average number of drinks per day, ranging from zero to more than five drinks per day. Alcohol was collapsed into two categories during analysis: $\leq$1 drink per day and >1 drink per day. The decision to combine consumption levels this way was made based on the U.S. Department of Agriculture's Dietary Guidelines for Americans 2015-2020 of $\leq$1 than one drink per day for women, a recommendation widely adopted in the U.S. (48). Smoking status defined was as current cigarette smoking (yes/no).

Self-reported genetic mutation diagnoses were first analyzed separately for potential confounding and effect modification in the association between BMI and breast and ovarian cancers. Specific breast cancer-linked genetic mutations/syndromes examined include *BRCA1/BRCA2*, Li-Fraumeni syndrome, Cowden Syndrome, Hereditary Diffuse Gastric and Lobular Breast Cancer Syndrome (HDGLBC), Peutz-Jeghers Syndrome (PJS), *PALB2*, *CHEK2*, *ATM*, *NBN*, and *BARD1*. Ovarian cancer-linked genetic mutations/syndromes examined include *BRCA1/BRCA2*, PJS, *BARD1*, *BRIP1*, *RAD51C*, *RAD51D*, and lynch syndrome. Due to the small sample size in some categories, diagnoses relating to each cancer were also pooled together to assess whether interaction existed between BMI and having any genetic mutation in the association between BMI and breast and ovarian cancers.

Other covariates included in the analysis were family history, polycystic ovarian syndrome (PCOS), endometriosis, age at menarche, and genetic testing status. Family history for breast or ovarian cancer was defined as having any immediate family members (parents, siblings, or children) been diagnosed with breast cancer at age $\leq$50, triple negative breast cancer, more than one breast cancer (cancer in both breasts, or two separate breast cancers in one breast), male breast cancer, ovarian cancer, primary peritoneal cancer, fallopian tube cancer, or having two or more close relative diagnosed with breast cancer at any age. Criteria for having a family history of breast or ovarian cancer was determined based on AYR logic and NCCN guidelines on Genetic/Familial High-Risk Assessment (49). Genetic testing status was a categorical variable with the following levels: self-tested positive, self-tested negative, self not tested with no relatives who tested positive, self not tested with relative(s) who tested positive.

Age at menarche was categorized as <12 or ≥12 years of age at first menstrual onset. PCOS and endometriosis were defined as personal health history of the corresponding condition.

Data analysis was completed using SAS® University Edition (v9). Descriptive statistics (means and frequencies) were calculated to compare the cases and controls in terms of demographics, health behaviors, personal health history, genetic mutation status, and other factors of interest. Logistic regression was used to model the association between BMI categories (exposure) and personal-history of breast or ovarian cancer (outcomes). The two outcomes were modelled separately. To assess for confounding, we first used the χ^2 test to determine which factors were associated with both the exposure and the outcomes at the α=0.05. We then individually added factors that met these criteria to logic regression models with BMI and the outcome of interest. Confounding was determined by either ≥10% change in the adjusted odds ratio compared to the crude. Effect modification was also assessed. Interaction terms of potential effect modifiers (EMs) were individually added to each breast and ovarian cancer model. The criteria for selecting EMs was based the significance of the interaction term with BMI, with significance defined as α=0.10.

To build the final models, we first included all confounders determined in the previous steps of the analysis. Variables independently associated with the outcome at the α=0.05 level were then added one by one to the multivariable models. Only independent predictors that significantly improved model fit, determined using the Akaike information criterion (AIC) and the likelihood-ratio test (LRT), were included in the final multivariable model. The fit of the final breast and ovarian cancer models were also assessed using the Hosmer-Lemeshow (HL) test. The significance of potential EMs identified in previous steps of the analysis was reassessed in

the final multivariable models at the α=0.10 level. We then stratified the final models by genetic and lifestyle factors that were determined to be effect modifiers to better examine their effects on the association between BMI and breast and ovarian cancers.

Results

Study Population Characteristics

The final study population included 1511 cases and 6045 controls for breast cancer, and 1267 cases and 5071 controls for ovarian cancer. Each study population included 310 individuals who reported personal history of both breast and ovarian cancer. Cases and controls had the same age distribution within each cancer study population.

The distribution of demographic and non-genetic risk factors of the breast and ovarian cancer study populations are summarized in Table 1. Most women in the breast cancer population were in the 36-40 age group (43.8%). There were significant differences between breast cancer cases and controls in BMI, exercise, age at menarche, oral contraceptive use, current smoking status, alcohol consumption, endometriosis, and genetic testing status. Compared to controls, more cases had a BMI in the underweight range, engaged in exercise at least 30 min/day, 5 days/week, experienced menstrual onset before 12 years of age, used or intend to use oral contraceptives for ≥5 years between 20-30 years of age, were current smokers, consumed >1 alcoholic beverage daily, and completed genetic testing (both positive and negative). More controls had a BMI in the obese range compared to cases. Personal history of PCOS and family history of breast cancer were not significant related to having a breast cancer diagnosis in the breast cancer population. Most women in the breast cancer study

population, 91.7% of the cases and 92.3% of the controls, reported having a family history of breast or ovarian cancer.

Most women in the ovarian cancer population were in the 20-30 age group (45.1%). There were significant differences between ovarian cancer cases and controls in all the variables listed in Table 1 with the exception of family history. Compared to controls, more cases reported BMI in the underweight and obese categories, exercised at least 30 min/day, 5 days/week, experienced menstrual onset before 12 years of age, were current smokers, consumed >1 alcoholic beverage daily, had a personal history of PCOS and endometriosis, and completed genetic testing. A larger proportion of controls reported BMI in the normal range and oral contraceptive use (or intention to use) for $\geq$5 years compared to the cases. Similar to women in the breast cancer population, 94.3% and 93.0% ovarian cancer cases and controls reported family history breast or ovarian cancer.

Self-reported diagnoses of genetic mutations and syndromes by case-control status are shown in Table 2. A total of 2.8% (212/7556) of the breast cancer population was found to have a diagnosed breast cancer-linked genetic mutation or syndrome, including LFS, Cowden syndrome, HDGLBC, PJS, *PALB2*, *CHEK*2, *ATM*, *NBN*, *BARD1*, or *BRCA1/BRCA2*. The majority of this 2.8% of the population had a *BRCA1/BRCA2* mutation (162/212). The proportion of women diagnosed with any genetic mutation was significantly higher among cases than controls. This same pattern was seen across all of the hereditary cancer mutations and syndromes listed in Table 2 with p-values <0.001.

For ovarian cancer, 0.9% (59/6331) of the study population had an ovarian-cancer linked genetic mutation or syndrome, including PJS, *BARD1*, *BRIP1*, *RAD51C*, *RAD51D*, *BRCA1/BRCA2*,

or Lynch syndrome. Fifty-three of the fifty-nine individuals reported a *BRCA1/BRCA2* mutation. The proportion of women diagnosed with any genetic mutation was significantly higher among cases than controls. The same trend was consistent across all specific hereditary mutations and syndromes reported in Table 2 with p-values <0.001.

Model Building – Association Between BMI and Breast & Ovarian Cancers

All of the variables shown in Table 1 met the definition for confounding in the association between BMI and breast cancer (associated with both exposure and outcome at the 0.05 α level) with the exception of PCOS and family history. Among variables that met the definition, only exercise altered the association between BMI and breast cancer by ≥10% and was adjusted for in the final model as a potential confounder. The final model for breast cancer also included smoking status, alcohol consumption, age at menarche, and genetic mutation status (any genetic mutation/syndrome diagnosis) as covariates, all of which were significantly related to breast cancer in the multivariable model with p-values <0.05. Covariates were only added if it improved the model fit based on a significant LRT and smaller AIC value. The HL test for the final model indicated there was no lack of fit (χ^2=12.88, p=0.116).

All variables listed in Table 1 other than family history met the definition for confounding in the association between BMI and ovarian cancer. Among variables that met the definition, PCOS altered the association by ≥10% and was adjusted for in the final model as a potential confounder. The final model for ovarian cancer also included exercise, smoking status, age at menarche, endometriosis, and genetic mutation status as covariates (p<0.05). Each covariate added significantly improved the model fit as indicated by a significant LRT test and

decrease in the AIC value. The HL test for the final model indicated there was no lack of fit (χ^2=7.82, p=0.452).

Association Between BMI and Breast and Ovarian Cancers

Table 3 shows the crude and adjusted odds ratios of BMI and breast and ovarian cancers**.** BMI was inversely associated with personal history of breast cancer after adjusting for exercise, smoking status, alcohol consumption, age at menarche, and genetic mutation status (p<0.001). Compared to women in the normal weight group, women in the underweight group were more likely to report personal history of breast cancer ($OR_{adjusted}$ 95% CI=1.31 [1.05, 1.64]), while women in the obese group were less likely have a personal history of breast cancer ($OR_{adjusted}$ 95% CI=0.82 [0.70, 0.96]). There was a small, non-significant reduction in past breast cancer diagnosis among the overweight group compared to the normal weight group ($OR_{adjusted}$ 95% CI=0.93 [0.79, 1.08]). As suggested by the crude ORs listed in Table 3, a similar inverse association with greater magnitude was observed between BMI and breast cancer prior to adjustment for confounders and covariates.

For ovarian cancer, the crude OR values suggested a J-shaped relationship between BMI and personal history of ovarian cancer prior to adjustment for confounders and covariates (p<0.001). Women in the underweight, overweight, and obese groups had significantly higher odds of past ovarian cancer diagnosis compared to the normal weight group (OR_{crude} 95% CI=2.06 [1.64, 2.58], 1.26 [1.06, 1.49], 1.48 [1.27, 1.71], respectively). BMI remained significantly associated with ovarian cancer after adjusting for PCOS, exercise, smoking status, age at menarche, endometriosis, and genetic mutation status in the final model, although a

graded association was no longer observed (p<0.001). Compared to women in the normal weight group, only women in the underweight group were significantly more likely to have a past breast cancer diagnosis ($OR_{adjusted}$ 95% CI=1.69 [1.32, 2.15]). The overweight and obese groups had slightly higher odds of past ovarian cancer diagnosis that was non-significant at the 0.05 level compared to the normal weight group ($OR_{adjusted}$ 95% CI=1.15 [0.96, 1.38], 1.16 [0.98, 1.37], respectively).

Effects of Genetic and Lifestyle Risk Factors on the E-D Relationships

Genetic and lifestyle risk factors that had significant interactions terms with BMI (p<0.10) in the final breast cancer model included physical activity, alcohol consumption, and smoking status (Table 4). The interaction term between any diagnosed genetic mutation was close to reaching statistical significance (p=0.13). Table 4 shows the association between BMI and breast cancer stratified by physical activity, alcohol consumption, smoking status, and genetic mutation status.

Among the 212 women diagnosed with breast cancer-linked gene mutations, BMI was not significantly associated with personal history of breast cancer (p=0.107). An inverse association between BMI and breast cancer was observed among women without diagnosed breast cancer-linked gene mutations (p<0.001).

Among women who reported exercising regularly, current smoking, or having >1 drink per day, underweight was associated with increased personal history of breast cancer ($OR_{adjusted}$ 95% CI=1.75 [1.28, 2.39], 2.07 [1.30, 3.30], 1.87 [1.23, 2.86], respectively). There were no significant differences in the odds of having a past breast cancer diagnosis between the

underweight and normal weight groups among women who did not exercise regularly, were non-smokers, or consumed ≤1 drink per day ($OR_{adjusted}$ 95% CI=0.92 [0.66, 1.30], 1.07 [0.82, 1.41], 1.14 [0.87, 1.50], respectively).

Having an overweight or obese BMI was not related to significant differences in breast cancer diagnosis relative to the normal weight group among women who exercised regularly ($OR_{adjusted}$ 95% CI=0.97 [0.77, 1.22], 0.91 [0.70, 1.18]), or consumed more than drink per day ($OR_{adjusted}$ 95% CI=1.03 (0.75, 1.40], 1.07 [0.77, 1.48]). Among women who did not exercise regularly, consumed ≤1 drink daily, or were not current smokers, BMI was inversely associated with personal history of breast cancer with the obese groups having significantly lower odds of past breast cancer diagnosis compared to the normal weight groups ($OR_{adjusted}$ 95% CI=0.76 [0.63, 0.92], 0.76 [0.63, 0.90], 0.81 [0.68, 0.96], respectively). For current smokers, the underweight group was less likely than the normal weight group to have a past breast cancer diagnosis ($OR_{adjusted}$ 95% CI=0.55 [0.36, 0.84]), but this protective effect did not reach significance for the obese group ($OR_{adjusted}$ 95% CI=0.81 [0.56, 1.17]).

Lifestyle factors that reached significance at the 0.10 level for interaction in the final ovarian cancer model include exercise, smoking status, and alcohol use. The interaction term between BMI and genetic mutation was not significant in the final model (p=0.9988). Table 5 shows the association between BMI and ovarian cancer stratified by exercise, smoking status, and alcohol use.

Among women who reported exercising regularly, current smoking, or having >1 drink per day, underweight was associated with significantly increased past ovarian cancer diagnosis ($OR_{adjusted}$=2.18 [1.51, 3.15], 1.92 [1.23, 3.01], 2.94 [1.80, 4.80], respectively). The same overall

association was observed with smaller effect sizes among women who were not exercising regularly, not current smokers, and had ≤1 drink per day ($OR_{adjusted}$ 95% CI =1.33 [0.96, 1.85], 1.52 [1.13, 2.06], 1.40 [1.05, 1.86], respectively).

Having an overweight or obese BMI was associated with higher, but non-significant odds of past ovarian cancer diagnosis compared to the normal weight group among women who engaged in regular physical activity ($OR_{adjusted}$ 95% CI=1.33 [1.00, 1.76], 1.33 [0.99, 1.72]). The same association was observed among overweight and obese women who have >1 drink per day ($OR_{adjusted}$ 95% CI = 1.15 [0.79, 1.66], 1.25 [0.86, 1.81]) and ≤1 drink per day ($OR_{adjusted}$ 95% CI=1.15 [0.94, 1.42], 1.14 [0.94, 1.37]). Among current-smokers, the overweight and obese groups had lower (but non-significant) odds of past ovarian cancer diagnosis compared to the normal weight group ($OR_{adjusted}$ 95% CI=0.77 [0.54, 1.10], 0.92 [0.67, 1.25]), while the overweight and obese groups who did not smoke were significantly more likely to have a personal history of ovarian cancer than normal weight women who did not smoke ($OR_{adjusted}$ 95% CI=1.33 [1.08, 1.64], 1.27 [1.04, 1.55]).

Association Between Other Risk Factors and Breast and Ovarian Cancers

The association between other covariates and breast and ovarian cancers in the final models are shown in Table 6. In the Bright Pink population, regular physical activity, current smoking, consuming ≥ 1 drink per day, menstrual onset <12 years of age, and having a diagnosed breast cancer-linked gene mutation were associated with increased personal history of breast cancer ($OR_{adjusted}$ 95% CI=1.50 [1.33, 1.70], 1.42 [1.21, 1.67], 1.28 [1.11, 1.47], 1.15 [1.01, 1.31], 36.08 [23.25, 55.99], respectively) after adjustment for all other variables in the

final breast cancer model. Regular physical activity, current smoking, menstrual onset <12 years of age, endometriosis, having a diagnosed ovarian cancer-linked gene mutation, and PCOS were on associated with increased personal history of ovarian cancer ($OR_{adjusted}$ 95% CI=1.41 [1.22, 1.62], 3.43 [2.96, 3.97], 1.44 [1.25, 1.65], 2.92 [2.45, 3.48], 7.84 [4.25, 14.47], 1.92 [1.62, 2.28], respectively) after adjustment for all other variables in the final ovarian cancer model.

Discussion

The results of the study suggest that BMI was inversely associated with personal history of breast cancer among women 20-40 years of age in the Bright Pink AYR population. In addition, having an underweight BMI was associated with increased past ovarian cancer diagnosis while having an overweight or obese BMI was associated with non-significant increases in past ovarian cancer diagnosis compared to the normal weight group. The associations between BMI and breast and ovarian cancers cancer were both modified by physical activity, alcohol consumption, and current smoking. Women in the underweight group appear particularly susceptible to the adverse effects of smoking, alcohol consumption, and possible excessive physical activity in relation to breast and ovarian cancer outcomes. The interaction between BMI and other behavioral risk factors of breast and ovarian cancers may contribute to the inconsistency of these associations observed in literature.

For breast cancer, our finding that higher BMI was protective of premenopausal breast cancer among women 20-40 years of age is consistent with recent findings in literature.[8-11, 50] In a 2014 meta-analysis of 89 epidemiological studies, Munsell et al. reported a 22% decreased risk of developing receptor-positive breast cancer for premenopausal women with BMI$\geq$ 30

compared to <25 kg/m^2.[11] A more recent prospective analysis of over 700,000 premenopausal women by the Premenopausal Breast Cancer Collaborative Group also reported a negative association between BMI and breast cancer. Similar to our findings, the greatest risk reduction was observed in comparing women in the highest (BMI$\geq$35.0 kg/m^2) and lowest BMI (<17.0 kg/m^2) groups (HR=0.24).[8] Studies have also reported findings that were discrepant to ours. Metanalyses conducted by Cheraghi et al. and Chen et al. both reported that higher BMI was not significantly associated with lower breast cancer incidence among premenopausal women.[51, 52] One possible explanation for this discrepancy is the adjustment of different risk factors and variations in population characteristics across studies, which may have resulted in null associations when pooled together in a meta-analysis. As shown in our analysis, the association between BMI and breast cancer can be substantially altered when stratified by a specific behavioral factor.

For ovarian cancer, the results from our analysis were different but not inconsistent with other findings reported in literature. Previous studies have mostly reported either a positive or lack of association between BMI and ovarian cancer among premenopausal women.[12, 13, 53, 54] Our results suggest that while higher BMI may be associated with a slightly higher odds of having ovarian cancer, having an underweight BMI was associated with significantly greater odds of ovarian cancer diagnosis relative to the normal weight group. One reason for this difference is that a number of meta-analyses only compared the ovarian cancer risk of women who were overweight and obese relative to the normal group, without including the underweight group in their pooled analysis.[53,54] Additionally, the adjustment for varying risk factors across studies may have contributed to the inconsistent associations observed between

BMI and ovarian cancer in literature. As demonstrated in our study, adjusting for PCOS, physical activity, smoking status, age at menarche, endometriosis and genetic mutation-carrier status substantially attenuated the increased odds of ovarian cancer among women with overweight and obese BMIs observed prior to adjustment.

The relationship between BMI and breast cancer may vary by genetic mutation-carrier status as suggested by the small p-value almost reaching statistical significance. As implicated by the wide OR confidence intervals after stratifying by genetic-mutation status, we were underpowered to accurately detect the effect size of the association between BMI and breast cancer among individuals with hereditary genetic mutations. Similarly, the small number of participants with diagnosed genetic mutations in the ovarian cancer population may have limited our ability to detect any significant interaction between BMI and genetic mutation diagnosis for ovarian cancer. Studies that have examined the relationship between BMI and breast cancer among *BRCA1/BRCA2* carriers have reported conflicting results.[14-17] Two mendelian randomization studies reported inverse associations between genetically predicted BMI, observed BMI, and premenopausal breast cancers among *BRCA1/BRCA2* carriers.[16, 17] In a recently published prospective cohort study, Kim et al. reported no observed association between BMI at age 18 and risk of pre-menopausal breast cancer among *BRCA1/BRCA2* carriers.[15] Moreover, researchers have also proposed that obesity increases breast cancer penetrance among *BRCA1/BRCA2* mutation carriers – which would implicate a positive association between BMI and increased breast cancer risk among *BRCA* carriers.[55] The results in our analysis combined with the inconsistencies in literature suggest there may exist a gene-

environment interaction between hereditary genetic mutations and BMI in breast cancer development which warrant further investigation.

Regular physical activity defined as exercising ≥30 minutes/day, 5 days/week, was associated with increased past breast and ovarian cancer diagnoses in Bright Pink AYR population. In comparison, the opposite association for physical activity and breast cancer has been reported in literature while the findings for ovarian cancer remain inconclusive.[23, 24, 36, 56, 57] There has also been evidence suggesting that the protective effects of physical activity only exist for post- but not pre-menopausal breast cancer.[34] One explanation for the discrepancy observed in our study for breast cancer is the possibility of reverse causation, a limitation of the case-control analysis. Young women who are breast or ovarian cancer survivors may be more health conscious and exercise more frequently. Additionally, the breast cancer case population may contain a greater proportion of women who engage in regular physical activity compared to all women diagnosed with the disease because physical activity has been linked to improved survival among breast cancer patients.[58] An alternative explanation is that women who met the definition of physical activity in our study are over-exercising. The intensity of exercise was not specified in the AYR questionnaire which limits our insight on the actual physical activity level of the responder. The stratified results for breast and ovarian cancers support this explanation. The "adverse effects" of physical activity for cancer outcomes were most distinguished among underweight women, a population more susceptible to engaging in unhealthy weight-control behavior such as excessive physical activity.[59] This is consistent with results observed in a prospective cohort study among Swedish twins, where physical activity was found to be

protective of premenopausal breast cancer among women who were overweight but not women who were underweight.[60]

Current smoking was associated with increased personal history of breast and ovarian cancers in the Bright Pink AYR population. The findings for breast cancer was consistent with that observed in literature while the association between smoking and ovarian cancer have been inconclusive and reported to vary by cancer subtype in other studies.[28, 29, 35, 37, 61] We were unable to analyze ovarian cancer outcomes by histological type as a limitation of the data collected in the AYR. The association between BMI and breast and ovarian cancers were both modified by cigarette smoking. There are limited data available in literature for these interactions. One cohort study reported that the risk of postmenopausal breast cancer was elevated in non-obese women (HR=1.25, 95% CI: 1.05, 1.47) but not among women who were obese (HR=0.96, 95% CI: 0.69, 1.34).[62] This does not contradict our finding that underweight women who smoked had more ovarian cancer diagnosis than the normal weight group but women who were obese and smoked did not. However, the breast cancer diagnoses in our study were most likely premenopausal and may be different from postmenopausal breast cancer in etiology. Among current smokers, women who were underweight also had the highest odds of past ovarian cancer diagnosis relative to the normal weight group, an effect that was attenuated among non-smokers. One explanation for the apparent higher susceptibility to breast and ovarian cancers observed among underweight women could be that there is less adipose tissue protection from the carcinogenic effects of tobacco smoke in these individuals.[28] Underweight women who smoke may also have more past breast and ovarian

cancer diagnoses because they are heavier smokers – a behavioral factor linked to lower BMI across epidemiological studies.[63]

Consuming >1 alcoholic drink per day was positively associated with personal history of breast but not ovarian cancer in the Bright Pink AYR population after adjusting for other covariates. The relationships observed are consistent with findings reported in literature for both cancers.[5, 23, 25, 35, 42-44] There were evidence of effect modification by level of alcohol consumption in the associations between BMI and both breast and ovarian cancers. Similar to the results observed for cigarette smoking, the underweight group appear to be particularly susceptible to the adverse effects of alcohol consumption in breast cancer development. Among women who consumed >1 drink per day, only the underweight group had significantly higher odds of personal breast cancer history relative to the normal weight group. Moreover, the same effect was not observed among women who consumed $\leq$ 1 drink per day. Similar findings have been reported in literature where elevated breast cancer risk associated with alcohol consumption was only observed among women with low BMI – defined as 25 kg/m^2 and <22.5 kg/m^2 in two different studies.[30, 31] But studies have reported non-significant interactions between BMI and alcohol use in breast cancer development.[32, 64] One reason for the discrepancies observed is that BMI and alcohol consumption were categorized differently across studies. Depending on these definitions, any excess drinking behavior in the underweight group compared to the other weight groups may not be captured. In other words, instead of being more susceptible to any carcinogenic effects of alcohol, it is also possible that the underweight group is at higher risk for breast cancer because they drink more than the other groups. However, the higher odds of ovarian cancer diagnosis observed among underweight

women who consume >1 drink per day supports the susceptibility hypothesis because alcohol consumption was not associated ovarian cancer prior to stratification.

Strengths & Limitations

In this analysis, we were able to examine the effect of a number of indeterminate and established risk factors on the associations between BMI and breast and ovarian cancers among women 20-40 years of age. We used standardized BMI categories to demonstrate the heightened effects alcohol consumption and smoking on breast and ovarian cancer outcomes among underweight women. To minimize confounding, we tested a large number of variables for potential confounding and frequency matched cases and controls by age. Additionally, the study population sampled was at higher average risk for breast and ovarian cancers compared to the general population, a group in which the relationship between BMI and these outcomes has not been well studied.

The study also had a number of limitations. First, this was a case-control analysis which implicate that the findings of the study are subject to reverse causality and should be interpreted with caution. However, other prospective studies have observed similar associations which contributes to the potential validity of the results. Second, self-reported measurements are often not reliable which may have introduced recall bias in the associations observed. Studies have reported tendencies for both young adults and adults to underreport their weight.[65, 66] Cases diagnosed with breast or ovarian cancers may monitor their weight more closely and less likely to underreport their BMIs compared to the controls. In our study, this would have biased the association with breast cancer toward the null since lower, rather

than higher BMI was associated with increased cancer diagnosis. That being said, more accurate recall or reporting of health behaviors by cases could have magnified the associations of these factors with breast and ovarian cancers. Third, the Bright Pink AYR population is likely at higher risk for breast and ovarian cancers compared to the general population which could limit the generalizability of the findings. Fourth, the study population was restricted to women between 20-40 years of age as an effort to examine the relationship of interest among premenopausal women only. However, we acknowledge that age is not a perfect predictor of menopausal status. Fifth, our data was limited by the degree of detail collected in the AYR. For example, we were unable to assess ovarian cancer outcomes by histological type or identify women who were engaging in excessive levels of physical activity. Lastly, we were not powered to examine interaction between specific gene mutations and BMI. This may be a limitation in many studies because the population prevalence of most breast and ovarian cancer-linked hereditary gene mutations are very low.[67-69]

Overall findings & public health implications

Having an underweight BMI was associated with more breast and ovarian cancer diagnosis among women who engage in regular (possibly excessive) physical activity, currently smoke, and consume >1 drink daily. These findings support the hypothesis that breast and ovary tissues may be particularly susceptible to adverse environmental exposures during development and excess adipose tissue among women with obese BMIs may be protective of these exposures. Regardless of the biological pathway, it appears that being underweight may have adverse effects in pre-menopausal breast and ovarian cancer development and women in

that weight group should be cautious in maintaining a healthy BMI. The majority of public health efforts in the past years have been focused on reducing obesity, and understandably so. Our study, along with other recent reports of inverse associations between BMI and premenopausal breast cancer in literature, reinforce the need to avoid BMI extremes on either end of the spectrum. Public health efforts can be important in promoting healthy body image, maintaining normal weight, and eliminating unhealthy weight control behaviors among adolescent and young women. In addition, reducing certain adverse health behaviors including smoking and excess alcohol consumption may help prevent premenopausal breast and ovarian cancers in addition to other health outcome benefits.

In line with previous findings, an inverse association was observed between BMI and premenopausal breast cancer diagnosis in the Bright Pink AYR population. However, this does not implicate promotion of weight gain among adolescent and young women in the normal weight group as obesity is strongly linked to many other morbidities later in life. The results of the study emphasis the importance of avoiding being underweight rather than promotion of having overweight or obese BMIs.

Conclusions

This is an exploratory analysis of interaction between BMI and several genetic and behavioral potential risk factors. The results of the study suggest that underweight women may have higher susceptibility to carcinogenic effects of environmental exposures but are subject to reverse causality and recall bias. Future prospective studies are necessary to verify these findings.

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Tables and Figures

Table 1. Study population characteristics by case-control status for breast and ovarian cancers.

Variable	Level	Breast cancer N=1511	No breast cancer N=6045	χ^2 statistic (p-value)[1]	Ovarian cancer N=1267	No ovarian cancer N=5071	χ^2 statistic (p-value)[1]
BMI (kg/m²)				35.62 (<0.0001)			50.34 (<0.0001)
	<18.5	145 (9.6)	376 (6.2)		138 (10.9)	342 (6.7)	
	18.5-24.9	610 (40.4)	2275 (37.6)		403 (31.8)	2054 (40.5)	
	25-29.9	363 (24.0)	1472 (24.4)		277 (21.9)	1123 (22.2)	
	30+	393 (26.0)	1922 (31.8)		449 (35.4)	1552 (30.6)	
Age				0.00 (1.000)			0.00 (1.000)
	20-30	403 (26.7)	1612 (26.7)		572 (45.1)	2289 (45.1)	
	31-35	447 (29.6)	1788 (29.6)		376 (29.7)	1505 (29.7)	
	36-40	661 (43.8)	2645 (43.8)		319 (25.2)	1277 (25.2)	
EXERCISE				57.94 (<0.0001)			7.92 (0.0049)
	Yes	676 (44.7)	2068 (34.2)		510 (40.3)	1825 (36.0)	
	No	835 (55.3)	3977 (65.8)		757 (59.8)	3246 (64.0)	
FIRST MENSTRUAL AGE				5.25 (0.0220)			59.67 (<0.0001)
	<12	497 (32.9)	1805 (29.9)		524 (41.4)	1522 (30.0)	
	≥12	1014 (67.1)	4240 (70.1)		743 (58.6)	3549 (70.0)	
OCP USE 5+ YEARS				4.06 (0.0439)			4.57 (0.0325)
	Yes	960 (63.5)	3670 (60.7)		737 (58.2)	3116 (61.5)	
	No	551 (36.5)	2375 (39.3)		530 (41.8)	1955 (38.6)	
SMOKE				27.40 (<0.0001)			374.33 (<0.0001)
	Yes	294 (19.5)	850 (14.1)		474 (37.4)	700 (13.8)	
	No	1217 (80.5)	5195 (85.9)		793 (62.6)	4371 (86.2)	
ALCOHOL				29.05 (<0.0001)			7.65 (0.0057)
	0-1	1111 (73.5)	4829 (79.9)		955 (75.4)	4004 (79.0)	
	1+	400 (26.5)	1216 (20.1)		312 (24.6)	1067 (21.0)	
PCOS				0.10 (0.7512)			139.72 (<0.0001)
	Yes	177 (11.7)	726 (12.0)		317 (25.0)	605 (11.9)	
	No	1334 (88.3)	5319 (88.0)		950 (75.0)	4466 (88.1)	
ENDOMETRIOSIS				9.32 (0.0023)			269.52 (<0.0001)
	Yes	178 (11.8)	555 (9.2)		311 (24.6)	413 (8.1)	
	No	1333 (88.2)	5490 (90.8)		956 (75.5)	4658 (91.9)	
FAMILY HISTORY				0.78 (0.3781)			2.91 (0.0879)
	Yes	1385 (91.7)	5582 (92.3)		1195 (94.3)	4717 (93.0)	
	No	126 (8.3)	463 (7.7)		72 (5.7)	354 (7.0)	
GENETIC TESTING STATUS[2]				3274.53 (<0.0001)			507.95 (<0.0001)
	S(-)	696 (46.1)	128 (2.12)		153 (12.1)	93 (1.8)	
	NT/R(-)	560 (37.1)	5667 (93.8)		954 (75.3)	4740 (93.5)	
	NT/R(+)	45 (3.0)	215 (3.6)		83 (6.6)	209 (4.1)	
	S(+)	210 (13.9)	35 (0.6)		77 (6.1)	29 (0.6)	

[1]χ^2 test used to evaluate significance at the 0.05 level.

[2]Genetic testing coded as follows:

S(-): self=tested negative

NT/R(-): self=not tested, relative=negative or not tested

NT/R(+): self=not tested, relative=tested positive

S(+): self=tested positive

Table 2. Genetic syndrome diagnosis in study population by case-control status for breast and ovarian cancers.

Gene mutation	Level	Breast cancer N=1511	No breast cancer N=6045	χ^2 statistic (p-value)[1]	Ovarian cancer N=1267	No ovarian cancer N=5071	χ^2 statistic (p-value)[1]
HEREDITARY GENETIC MUTATION				652.00 (<0.0001)			97.59 (<0.0001)
	Yes	189 (12.5)	23 (0.4)		42 (3.3)	17 (0.3)	
	No	1322 (87.5)	6022 (99.6)		1225 (96.7)	5054 (99.7)	
Li-Fraumeni Syndrome				26.73 (<0.0001)			48.12 (<0.0001)
	Yes	8 (0.5)	2 (0.0)		8 (0.6)	0 (0.00)	
	No	1503 (99.5)	6043 (100.0)		1259 (99.4)	5071 (100.0)	
Cowden				54.52 (<0.0001)			52.14 (<0.0001)
	Yes	15 (0.7)	0 (0.0)		9 (0.7)	0 (0.00)	
	No	1496 (99.3)	6045 (80.1)		1258 (99.3)	5071 (100.0)	
PJS				26.73 (<0.0001)			26.75 (<0.0001)
	Yes	8 (0.5)	0 (0.0)		6 (0.5)	0 (0.0)	
	No	1503 (99.5)	6045 (100.0)		1261 (99.5)	5071 (100.0)	
PALB2				57.47 (<0.0001)			38.62 (<0.0001)
	Yes	14 (0.9)	1 (0.0)		8 (0.6)	0 (0.0)	
	No	1497 (99.1)	6044 (100.0)		1259 (99.4)	5071 (100.0)	
CHEK2				71.97 (<0.0001)			26.75 (<0.0001)
	Yes	19 (1.3)	2 (0.0)		7 (0.6)	0 (0.0)	
	No	1492 (98.7)	6043 (100.0)		1260 (99.5)	5071 (100.0)	
ATM				74.52 (<0.0001)			18.82 (<0.0001)
	Yes	20 (95.24)	0 (0.0)		5 (0.4)	2 (0.0)	
	No	1491 (19.79)	6045 (100.0)		1262 (99.6)	5069 (100.0)	
NBN				18.91 (<0.0001)			16.02 (<0.0001)
	Yes	6 (0.4)	0 (0.0)		4 (0.3)	0 (0.00)	
	No	1505 (99.6)	6045 (100.0)		1263 (99.7)	5071 (100.0)	
BARD1				30.67 (<0.0001)			22.82 (<0.0001)
	Yes	8 (0.5)	0 (0.0)		7 (0.6)	1 (0.0)	
	No	1503 (99.5)	6045 (100.0)		1260 (99.5)	5070 (100.0)	
BRIP1				18.80 (<0.0001)			20.03 (<0.0001)
	Yes	7 (0.5)	1 (0.0)		5 (0.4)	0 (0.00)	
	No	1504 (99.5)	6044 (100.0)		1262 (99.6)	5071 (100.0)	
RAD51C				26.32 (<0.0001)			19.16 (<0.0001)
	Yes	6 (0.4)	1 (0.0)		5 (0.4)	2 (0.0)	
	No	1505 (99.6)	6044 (100.0)		1262 (99.6)	5069 (100.0)	
RAD51D				30.14 (<0.0001)			26.75 (<0.0001)
	Yes	7 (0.5)	0 (0.0)		5 (0.4)	0 (0.0)	
	No	1504 (99.5)	6045 (100.0)		1262 (99.6)	5071 (100.0)	
BRCA1 BRCA2				375.08 (<0.0001)			44.34 (<0.0001)
	Yes	144 (9.5)	18 (0.3)		37 (2.9)	16 (0.3)	
	No	1367 (90.5)	6027(99.7)		1230 (97.1)	5055 (99.7)	
LYNCH SYNDROME				45.24 (<0.0001)			41.45 (<0.0001)
	Yes	14 (0.9)	1 (0.0)		10 (0.8)	1 (0.0)	
	No	1497 (99.1)	6044 (100.0)		1257 (99.2)	5070 (100.0)	

[1]χ^2 test used to evaluate significance at the 0.05 level.

Table 3. Logistic regression of personal history of breast and ovarian cancers on BMI

	Breast Cancer[1]			**Ovarian Cancer[2]**		
BMI	Total 7556	OR_{crude} (95% CI)	$OR_{adjusted}$ (95% CI)	Total 6338	OR_{crude} (95% CI)	$OR_{adjusted}$ (95% CI)
Underweight	521	1.44 (1.16, 1.78)	1.31 (1.05, 1.64)	480	2.06 (1.64, 2.58)	1.68 (1.32, 2.15)
Normal weight	2885	Reference	Reference	2937	Reference	Reference
Overweight	1835	0.92 (0.80, 1.06)	0.93 (0.79, 1.08)	4337	1.26 (1.06, 1.49)	1.16 (0.96, 1.38)
Obese	2315	0.76 (0.66, 0.88)	0.82 (0.70, 0.96)	6338	1.48 (1.27, 1.71)	1.16 (0.98, 1.37)
P-Trend		<0.001	<0.001		<0.001	<0.001

[1]Breast cancer final model adjusted for exercise, smoking status, alcohol use, age at menarche, genetic mutation-carrier status (any gene).
[2]Ovarian cancer final model adjusted for PCOS, exercise, smoking status, age at menarche, endometriosis, and genetic mutation-carrier status.

Table 4. Logistic regression of personal history of breast cancer on BMI stratified by genetic and lifestyle factors

Association between BMI and Breast Cancer ($OR_{adjusted}$, 95% CI)						
Genetic and Lifestyle Factors	Total 7127	Body Mass Index (BMI) Underweight	Normal weight	Overweight	Obese	*P-trend*
Genetic mutation[1]						
Yes	212	3.60 (0.44, 29.82)	Reference	5.22 (1.11, 24.55)	1.36 (0.47, 3.97)	0.107
No	7344	1.32 (1.03, 1.70)	--------	0.92 (0.78, 1.09)	0.80 (0.68, 0.94)	<0.001
*Interaction p-value**	0.131					
Exercise[2]						
Yes	2744	1.75 (1.28, 2.39)	--------	0.97 (0.77, 1.22)	0.91 (0.70, 1.18)	0.001
No	4812	0.92 (0.66, 1.30)	--------	0.88 (0.71, 1.08)	0.76 (0.63, 0.92)	0.042
Interaction p-value	0.014					
Smoking status[3]						
Yes	1144	2.07 (1.30, 3.30)	--------	0.55 (0.36, 0.84)	0.81 (0.56, 1.17)	<0.001
No	6412	1.07 (0.82, 1.41)	--------	1.01 (0.86, 1.19)	0.81 (0.68, 0.96)	0.043
Interaction p-value	<0.001					
Alcohol use[4]						
0-1	5940	1.14 (0.87, 1.50)	--------	0.89 (0.75, 1.06)	0.76 (0.63, 0.90)	0.004
1+	1616	1.87 (1.23, 2.86)	--------	1.03 (0.75, 1.40)	1.07 (0.77, 1.48)	0.029
Interaction p-value	0.043					

[1]Logistic regression model adjusted for exercise, smoking status, alcohol use, age at menarche, and stratified by diagnosis of any genetic mutation.
[2]Logistic regression model adjusted for smoking status, alcohol use, age at menarche, and stratified by exercise status, defined as engaging in physical activity at least 30min/day, 5 days/week.
[3]Logistic regression model adjusted for exercise, alcohol use, age at menarche, and stratified by smoking, defined by user self-reported current smoking status.
[4]Logistic regression model adjusted for exercise, smoking status, age at menarche, and stratified by alcohol use, defined as consuming more than one drink per day, on average.
*Interaction term significance with BMI in the final model determined at the 0.10 level.

Table 5. Logistic regression of personal history of ovarian cancer on BMI stratified by genetic and lifestyle factors

	Association between BMI and Ovarian Cancer ($OR_{adjusted}$, 95% CI)					
Genetic and Lifestyle Factors	**Total** 6338	**Body Mass Index (BMI)** Underweight	Normal weight	Overweight	Obese	*P-trend*
Exercise[1]						
Yes	2335	2.18 (1.51, 3.15)	Reference	1.33 (1.00, 1.76)	1.33 (0.99, 1.72)	<0.001
No	4003	1.33 (0.96, 1.85)	--------	1.02 (0.80, 1.29)	1.05 (0.85, 1.30)	0.384
*Interaction p-value**	0.086					
Smoking status[2]						
Yes	1174	1.92 (1.23, 3.01)	--------	0.77 (0.54, 1.10)	0.92 (0.67, 1.25)	0.002
No	5164	1.52 (1.13, 2.06)	--------	1.33 (1.08, 1.64)	1.27 (1.04, 1.55)	0.007
Interaction p-value	0.015					
Alcohol use[3]						
0-1	4959	1.40 (1.05, 1.86)	--------	1.15 (0.94, 1.42)	1.14 (0.94, 1.37)	0.113
1+	1379	2.94 (1.80, 4.80)	--------	1.15 (0.79, 1.66)	1.25 (0.86, 1.81)	<0.001
Interaction p-value	0.054					

[1]Logistic regression model adjusted for PCOS, smoke, age at menarche, endometriosis, genetic mutation diagnosis and stratified by exercise, defined as engaging in physical activity at least 30 min/day, 5 days/week.

[2]Logistic regression model adjusted for PCOS, exercise, age at menarche, endometriosis, genetic mutation diagnosis and stratified by smoking, defined by self-reported current smoking status.

[3]Logistic regression model adjusted for PCOS, exercise, smoking status, age at menarche, endometriosis, genetic mutation diagnosis stratified by alcohol use, defined as consuming more than one drink per day.

*Interaction term significance with BMI in the final model determined at the 0.10 level.

Table 6. Logistic regression of personal history of breast and ovarian cancer on other risk factors.

Risk Factors	**Breast Cancer[1]**	**Ovarian Cancer[2]**
	$OR_{adjusted}$ (95% CI)	**$OR_{adjusted}$ (95% CI)**
Exercise	1.50 (1.33, 1.70)	1.41 (1.22, 1.62)
Smoking status	1.42 (1.21, 1.67)	3.43 (2.96, 3.97)
Alcohol use	1.28 (1.11, 1.47)	-
Age at menarche	1.15 (1.01, 1.31)	1.44 (1.25, 1.65)
Endometriosis	-	2.92 (2.45, 3.48)
Genetic Mutation	36.08 (23.25, 55.99)	7.84 (4.25, 14.47)
PCOS	-	1.92 (1.62, 2.28)

[1]Logistic regression of breast cancer on BMI, exercise, smoking status, alcohol use, age at menarche, genetic mutation status.

[2]Logistic regression of ovarian cancer on BMI, PCOS, exercise, smoking status, age at menarche, endometriosis, and genetic mutation-carrier status.