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Adherence to the 2020 American Cancer Society Guideline for Cancer Prevention and risk of breast cancer for women at increased familial and genetic risk in the Breast Cancer Family Registry: An evaluation of the weight, physical activity, and alcohol consumption recommendations

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Abstract

Purpose—The American Cancer Society (ACS) published an updated Guideline for Cancer Prevention (ACS Guideline) in 2020. Research suggests that adherence to the 2012 ACS Guideline might lower breast cancer risk, but there is limited evidence that this applies to women at increased familial and genetic risk of breast cancer.

Methods—Using the Breast Cancer Family Registry (BCFR), a cohort enriched for increased familial and genetic risk of breast cancer, we examined adherence to three 2020 ACS Guideline recommendations (weight management (body mass index), physical activity, and alcohol consumption) with breast cancer risk in 9,615 women. We used Cox proportional hazard regression modeling to calculate hazard ratios (HRs) and 95% confidence intervals (CI) overall, and stratified by *BRCA1* and *BRCA2* pathogenic variant status, family history of breast cancer, menopausal status, and estrogen-receptor positive (ER+) breast cancer.

Results—We observed 618 incident invasive or *in situ* breast cancers over a median 12.9 years. Compared with being adherent to none (n=55 cancers), being adherent to any ACS recommendation (n=563 cancers) was associated with a 27% lower breast cancer risk (HR=0.73, 95% CI: 0.55–0.97). This was evident for women with a first-degree family history of breast cancer (HR=0.68, 95% CI: 0.50–0.93), women without *BRCA1* or *BRCA2* pathogenic variants (HR=0.71, 95% CI: 0.53–0.95), postmenopausal women (HR=0.63, 95% CI: 0.44–0.89), and for risk of ER+ breast cancer (HR=0.63, 95% CI: 0.40–0.98).

Discussion—Adherence to the 2020 ACS Guideline recommendations for BMI, physical activity, and alcohol consumption could reduce breast cancer risk for postmenopausal women and women at increased familial risk.

Keywords

Breast Cancer; Cancer Prevention; Incidence; Lifestyle behaviors

Introduction

In the USA, breast cancer is the most common female cancer and second most common cause of cancer death in women, with an estimated 281,550 new cases and 43,600 deaths to occur in 2021 [1]. Approximately 1 in 8 women (12.9%) will develop breast cancer in their lifetime, and the incidence rate continues to rise, particularly in women below 40 years [2, 3]. Given the high burden of breast cancer, identifying primary prevention methods is critical.

Women with a family history of breast cancer, or pathogenic variants in *BRCA1* or *BRCA2* (*BRCA1/2)*, or other genes such as *PALB2*, have a higher risk of developing breast cancer in their lifetime compared with the general population [4–8]. Further, research has shown family history matters even in *BRCA1/2* carriers. Compared with having no family history of breast cancer, having one first-degree relative with breast cancer is associated with a 39% and 21% increased risk of breast cancer for *BRCA1* and *BRCA2* carriers, respectively [6]. Given the higher risk of breast cancer for women with a familial or genetic predisposition, it is important to identify modifiable factors, beyond risk-reducing surgery, which reduces their risk.

In an effort to reduce the incidence and mortality of all cancers, the American Cancer Society (ACS) published cancer prevention guidelines called the ACS Guideline for Diet and Physical Activity for Cancer Prevention (ACS Guideline) [9, 10]. The ACS Guideline, updated in June 2020, includes four recommendations for cancer prevention based on weight, physical activity, diet, and alcohol consumption [10]. Prior studies have observed a 19–31% lower risk of breast cancer associated with adherence to the 2012 ACS Guideline [11–13]. However, these studies did not select women based on their underlying familial or genetic risk (non-enriched cohorts) and, therefore, were underpowered for examining whether ACS Guideline adherence modifies absolute and relative breast cancer risk in women at higher risk based on cancer family history and/or presence of pathogenic variants in *BRCA1/2* (enriched cohorts) [14]. Further, no studies to date have examined the association between the updated 2020 ACS Guideline. We examined adherence to the non-dietary components of the 2020 ACS Guideline in a large international enriched cohort, the Breast Cancer Family Registry (BCFR) [15]. We hypothesized that adherence to the weight, physical activity, and alcohol ACS Guideline recommendations would be associated with a lower breast cancer risk for women at increased familial and genetic risk of breast cancer.

Methods

Study Sample

We conducted a prospective cohort analysis using the BCFR, adhering to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Guidelines [16]. The BCFR consists of six sites across the USA, Canada, and Australia which recruited families across the spectrum of breast and ovarian cancer risk, beginning in 1996 [15]. Participants were enrolled through clinic-, community-, and population-based recruitment centers and followed at each site using a common protocol [15]. The BCFR includes women across the

risk spectrum with sufficient statistical power to test if risks differ by underlying genetic and familial risk [17–20]. Additional recruitment details are published elsewhere [14, 15].

Participants completed a baseline questionnaire, providing data on self-reported demographics (e.g., age, race and ethnicity), lifestyle (e.g., alcohol consumption, smoking, recreational physical activity), reproductive factors (e.g., parity, menopausal status), anthropometry (e.g., height, weight), medical history (e.g., cancer history, hormone use), and family history of cancer. Participants provided updated information on breast cancer risk factors and medical and family history through follow-up questionnaires. Participants also provided blood or saliva samples and were tested for *BRCA1/2* pathogenic variants, as detailed elsewhere [21, 22]. Typically, the youngest affected family member was tested and, if a *BRCA1/2* pathogenic variant was found, then other family members were tested; therefore, women not tested are assumed negative. Institutional Review Boards at each site approved the study and all participants provided written consent prior to enrollment.

ACS Guideline

The 2020 ACS Guideline has four components (weight management, physical activity, diet, and alcohol consumption). As 36.4% of the BCFR cohort did not complete the food frequency questionnaire, we assessed adherence based on the non-dietary components of the 2020 ACS Guideline detailed below.

Weight Management—The ACS Guideline states that it is ideal to keep body weight within a healthy range and to avoid gaining weight in adulthood [10]. We used self-reported baseline height and weight to calculate body mass index (BMI) at baseline [23]. We used the WHO BMI guidelines of 18.5 to <25.0 kg/m^2 to define healthy body weight and categorized women as adherent if they had a BMI in this range.

Physical Activity—The ACS Guideline recommends adults participate in 150 to 300 minutes of moderate-intensity or 75–150 minutes of vigorous-intensity physical activity per week, or a combination of both. Further, it states achieving or exceeding 300 minutes of physical activity per week is optimal [10]. At baseline, participants reported frequency (30, 60, 90, 120, 180, 240–360, 420–600, ≥660 minutes per week) of their recreational physical activity over the past three years, separately for moderate and strenuous activities. We categorized women as adherent if they reported ≥180 minutes of moderate or 90 minutes of strenuous physical activity per week. We conducted a sensitivity analysis categorizing women as adherent if they reported ≥300 minutes of moderate or strenuous physical activity per week.

Alcohol Consumption—The 2020 ACS Guideline recommends that it is best to not drink alcohol, but if alcohol is consumed to limit it to 1 drink per day for women [10]; however, the 2012 ACS Guideline recommendation limited alcohol consumption to 1 drink per day for women, and 1 drink was classified as 12 ounces of beer, 5 ounces of wine, or 1.5 ounces of 80-proof distilled spirits [9]. At baseline, participants reported how much beer, wine, and liquor they consumed at least once per week. We categorized women as adherent if they

reported not drinking alcohol at least once per week for 6 months or longer (defined as no alcohol).

Adherence score assessment

We used a previously published scoring method to measure ACS Guideline adherence [24]. Participants received 1 point for adherence to any of the three ACS Guideline recommendations, with the total score ranging from 0 to 3. We also conducted an analysis using the 2012 ACS Guideline, with alcohol adherence defined as consuming ≤7 drinks per week.

Exclusions

There were 24,117 participants identified for this analysis and exclusion criteria included breast cancer diagnosis prior to baseline (n=10,404), age ≥80 years at baseline (n=365), and person-time time less than 2 months (n=344). Additionally, women were excluded if they were missing data on adherence score variables (n=283 for BMI; n=597 for alcohol consumption, and n=2,509 for physical activity). Thus, 9,615 participants were included in our analytic sample. In order to examine possible selection bias, we compared differences in baseline characteristics between women who were excluded due to missing data on BMI, alcohol consumption, or physical activity, and women who were included.

Outcome Assessment

We included all prospective invasive and *in situ* breast cancers diagnosed more than two months after the baseline interview; the verification of breast cancers was previously described [15]. Briefly, breast cancer diagnoses were self-reported by participants and confirmation was obtained through pathology review, pathology reports, medical records, death certificates, or linkage to state cancer registries or the National Death Index (N=476, 77.0% confirmed). We conducted sensitivity analyses examining associations limited to confirmed cases, and excluding *in situ* breast cancers. We had limited estrogen receptor (ER) and progesterone receptor (PR) data available (50.6% missing) to evaluate differences by molecular subtype of breast cancer. However, we examined the association between ACS Guideline adherence and risk of ER positive breast cancer (n=230), the largest subtype.

Statistical Analysis

We calculated frequencies and percentages for categorical variables and means and standard deviations (SDs) for continuous variables overall and by ACS Guideline recommendation. We used Cox proportional hazard regression modeling to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between ACS Guideline adherence and risk of breast cancer [12, 23, 25, 26]. We used age as the underlying time scale and calculated person time from age of baseline interview to age at breast cancer diagnosis, bilateral mastectomy, death, last follow-up, or age 80 years, whichever came first. We assessed the proportional hazards assumption using the ASSESS statement in SAS; there were no statistically significant violations of this assumption. All models were stratified by birth cohort (<1950, 1950–1959, 1960–1969, ≥1970), and our multivariable models included the following variables which met the 10% change-in-beta criterion: race and

ethnicity (Asian, Hispanic, non-Hispanic Black, non-Hispanic White, other (defined as self-reported “American Indian, Aleutian, or Eskimo” or “other” groups)), education (high school graduation/GED or less, vocational or technical school/some college or university, bachelor’s degree or higher), cigarette use (never, former, current), oral contraceptive use (never, ever), menopausal hormone therapy use (never, ever), parity (none, 1–2 live births, ≥3 live births), breastfeeding (never, ever), and age at menarche (continuous). We stratified the analyses by *BRCA1/2* pathogenic variant status (*BRCA1/2* positive defined as being positive for a *BRCA1* or *BRCA*2 pathogenic variant, *BRCA1/2* negative defined as not having a pathogenic variant in either gene or not tested), family history of breast cancer (defined as having ≥1 first-degree relative with breast cancer to align with family history information commonly collected in the clinic to assess breast cancer risk, such as for the Breast Cancer Risk Assessment Tool [27]), menopausal status, and age at the baseline interview (<50, 50–60, >60 years), and examined effect measure modification (interaction) on the multiplicative scale using a cross-product term with the Wald test and on the additive scale using the relative excess risk due to interaction (RERI) [28]. We conducted the following additional sensitivity analyses: 1) excluding women with person-time time less than 1 year or 2 years, 2) creating a separate group for women not tested for *BRCA1/2* pathogenic variants, and 3) defining a positive family history as ≥1 first-degree relative or ≥2 second-degree relatives with breast cancer. For 470 (4.9%) participants menopausal status was missing and imputed based on the 90th percentile of age at natural menopause for smokers and non-smokers (age 55 years for both) [29], with postmenopausal status defined as age at baseline ≥55 years. All other variables had less than 2% missing data; therefore, we created a missing category for categorical variables and missing indicator variable for continuous variables to enhance statistical power. All statistical tests were performed using SAS 9.4 (SAS Institute, Inc. Cary, North Carolina).

Results

Baseline characteristics by ACS Guideline adherence score are presented in Table 1. From the total analytic sample (n=9,615), 618 (6.4%) developed incident invasive or *in situ* breast cancer (n=90 confirmed *in situ* breast cancers) over a median 12.9 years of follow-up (median time to breast cancer event was 6.9 years). The majority of women had an adherence score of 2 (44.2%) followed by a score of 1 (31.6%). For women with a score of 2, adherence to the alcohol and physical activity recommendations was the most common (42.6%). For women with a score of 1, adherence to the alcohol recommendation was the most common (45.3%), followed by physical activity (34.8%), and BMI (19.8%). Women with a score of 3 were on average younger, more likely to have a bachelor’s or graduate degree, more likely to be a never smoker, and more likely to have a mutation in *BRCA1/2*, compared with women with lower adherence scores. Baseline characteristics by adherence to individual ACS Guideline recommendations are presented in Supplemental Table 1. The mean age at baseline was 48.1 years, the mean age at diagnosis was 58.4 years, and the majority of women were non-Hispanic White (68.2%). There were 585 women (6.1%) with a known *BRCA1/2* pathogenic variant. For all of the ACS Guideline recommendations, there was a higher percentage of *BRCA1/2* carriers in the adherent versus not adherent group. To explore possible selection bias, we compared baseline differences between women included

in the analysis and excluded due to missing BMI, alcohol, and physical activity data (Supplemental Table 2). Compared with included women, excluded women were slightly younger at baseline and more likely to be non-Hispanic White. We also examined our results excluding women with 1 year or 2 years of person-time (Supplemental Table 3). Overall there were minimal differences in the results; however, in the analysis excluding person-time less than 2 years, the result for being adherent on 3 recommendations versus none was slightly stronger and statistically significant (HR=0.69, 95% CI: 0.48–0.98).

Associations between ACS Guideline adherence and breast cancer risk are shown in Table 2. Women who adhered to any versus none of the ACS Guideline recommendations had a 27% lower breast cancer risk (HR=0.73, 95% CI: 0.55–0.97). When we examined adherence to one, two, or three recommendations compared with none, we observed similar magnitudes of association and the p for trend was not statistically significant (p=0.12).

The 2020 and 2012 ACS Guideline recommendations evaluated in this analysis are presented in Supplemental Table 4. In Supplemental Table 5, we present baseline characteristics by adherence to the 2012 ACS Guideline alcohol recommendation. Notably, more women were adherent to the 2012 alcohol recommendation (87.6%) versus the 2020 recommendation (60.1%), reflecting the change in adherence from ≤7 drinks per week (2012) to no alcohol (2020). We examined the 2012 ACS Guideline with breast cancer risk (Supplemental Table 6). We observed a 47% lower breast cancer risk for women adhering to any versus none of the 2012 ACS Guideline recommendations (HR=0.53, 95% CI: 0.35–0.81), and there was a borderline statistically significant trend (p=0.06) when looking at adherence to one, two, or three recommendations. The adherence scores for the 2020 and 2012 ACS Guidelines were highly correlated ($r = 0.85$, $p<0.01$).

Table 3 shows HR estimates stratified by *BRCA1/2* pathogenic variant status, family history, and menopausal status. A sensitivity analysis which created a separate category for women not tested for *BRCA1/2* pathogenic variants showed similar results to the *BRCA1/2* negative group (data not shown); therefore, we combined these groups to enhance the statistical power. *BRCA1/2* negative women had a 29% lower breast cancer risk when adhering to any versus none of the ACS Guideline recommendations (HR=0.71, 95% CI: 0.53–0.95). While there was a suggestion of a lower breast cancer risk for *BRCA1/2* positive women, it was not statistically significant (HR=0.43, 95% CI: 0.16–1.20). We observed no association between ACS Guideline adherence and breast cancer risk in women without a first-degree family history of breast cancer. In contrast, women with at least one first-degree relative with breast cancer had a 32% lower breast cancer risk (HR=0.68, 95% CI: 0.50–0.93). However, we did not observe interaction on either the multiplicative or additive scales for *BRCA1/2* pathogenic variant status (p=0.33 and RERI=−2.46, 95% CI: −11.19–6.27) or family history (p=0.22 and RERI=−0.94, 95% CI: −2.80–0.91). When we examined family history defined as having ≥1 first-degree relative or ≥2 second degree relatives with breast cancer, the results were similar (data not shown). While we observed no association in premenopausal women, postmenopausal women who adhered to any versus none of the ACS Guideline recommendations had a 37% (HR=0.63, 95% CI: 0.44–0.89) lower breast cancer risk. However, we did not observe interaction on either the multiplicative (p=0.17) or additive (RERI=−0.37, 95% CI: −1.10–0.37) scales. We further explored differences by age

at baseline (Supplemental Table 7). We observed an association only in older women aged >60 years, with a 42% lower breast cancer risk for those who adhered to any versus none of the ACS Guideline recommendations.

Limiting the analysis to ER-positive breast cancers, women who adhered to any versus none of the ACS Guideline recommendations had a 37% lower risk of developing ER-positive breast cancer (HR=0.63, 95% CI: 0.40–0.98) (Table 4). In addition, we conducted sensitivity analyses excluding confirmed *in situ* breast cancers (Supplemental Table 8) and limited to only confirmed invasive and *in situ* breast cancers (data not shown) and observed minimal differences in results.

Using the more stringent definition of physical activity adherence (≥300 minutes of moderate or strenuous physical activity per week), 56.0% of women were adherent versus 63.7% of women using the original definition of physical activity adherence. While the results were similar, the association was slightly attenuated and borderline statistically significant for women who adhered to any recommendation versus none (HR=0.78, 95% CI: 0.60, 1.02) (Supplemental Table 9).

Discussion

We examined the association between adherence to the 2020 ACS Guideline recommendations for weight, physical activity, and alcohol consumption and breast cancer risk in a clinically-relevant cohort enriched for higher absolute breast cancer risk based on family history of breast cancer or pathogenic variants in *BRCA1/2*. Overall, we observed that a lower breast cancer risk was associated with adherence to any of the three non-dietary ACS Guideline recommendations. This lower risk was observed for women without *BRCA1/2* pathogenic variants, women with a first-degree family history of breast cancer, and postmenopausal women. While there was also a protective association for *BRCA1/2* positive women, it was not statistically significant likely due to a small number of breast cancer events in this stratum. While some who believe in genetic determinism might argue that the risk for women with a pathogenic variant is so high it cannot be modified by these behaviors, this is not supported by published studies using this cohort which have observed risk associations for women at increased genetic risk [17–19].

When examining the risk of breast cancer using the 2012 ACS Guideline, we observed a lower breast cancer risk with adherence to any of the three non-dietary recommendations versus none in this enriched cohort, which is similar to what prior studies have reported in non-enriched cohorts of mostly older women [11–13]. While these prior studies observed a statistically significant trend when examining extent of adherence, we did not observe this using the 2020 ACS Guideline which includes the change in alcohol recommendation for women from ≤7 drinks per week to no alcohol; however, our results using the 2012 ACS Guideline suggested an inverse trend but it did not reach statistical significance. We also found that a higher percentage of *BRCA1/2* carriers than non-carriers adhered to any ACS Guideline recommendation versus none which is consistent with what others have found with other risk management guidelines [30].

Previous work using one of the six BCFR sites observed a lower overall mortality for women who adhered to the 2012 ACS Guideline [23]; the present results suggest that the benefit could extend to a reduction in breast cancer risk. This is the first study to examine the 2020 ACS Guideline and breast cancer risk and the first to examine the association using a cohort of younger women enriched for higher breast cancer risk.

Our study had some limitations. We excluded 3,389 women (26.1%) missing data on BMI, alcohol consumption, or physical activity which may have introduced selection bias. However, there were minimal differences between women excluded versus included in the analysis, except that excluded women were slightly younger and more likely to be non-Hispanic White than included women. Since younger age is negatively associated with breast cancer risk but positively associated with adherence, excluding younger women may have biased our results away from the null; however, our results were stronger and only statistically significant in older women (postmenopausal and over the age of 60 years). We were unable to assess all four components of the ACS Guideline due to incomplete dietary data. However, a recent study observed no association between the 2012 ACS Guideline diet recommendation and breast cancer incidence [31], so it is possible to conclude that the omission of the diet recommendation did not materially affect our results. For the adherence score variable, we gave equal weight to the three ACS Guideline recommendations (BMI, alcohol consumption, and physical activity); however, it is likely these factors contribute differentially to breast cancer risk. Lastly, this study may have been underpowered to detect additive and multiplicative interaction.

The present findings, which are consistent with prior epidemiological studies in average-risk populations, confirm that adherence to the weight, physical activity, and alcohol consumption ACS Guideline recommendations might reduce breast cancer risk in postmenopausal women at increased familial risk. Many women from high-risk families fear that developing breast cancer is a matter of “when, not if”. Our findings reinforce the importance of educating all women, especially those with baseline-elevated risk who may feel there is little they can do to reduce their risk, that factors within their control could reduce their breast cancer risk. Furthermore, weight management, physical activity, and lowering alcohol intake could carry other health benefits without the negative aspects of risk-reducing approaches such as prophylactic surgeries and chemopreventive medications. In our cohort, adherence to the ACS Guideline was higher for younger versus older women and primary care doctors could actively encourage young women to continue these behaviors throughout the lifecourse. Future research should try to replicate these results for high-risk women, including the dietary component of the ACS Guideline, using larger cohorts of racial and ethnic minority populations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1:

Baseline characteristics of women in the Breast Cancer Family Registry by adherence score for the American Cancer Society Guideline for Cancer Prevention recommendations on weight, physical activity, and alcohol consumption

	Adherence Score (n=9,615)							
	0 (n=624)		**1 (n=3,034)**		**2 (n=4,251)**		**3 (n=1,706)**	
	6.5%		**31.6%**		**44.2%**		**17.7%**	
Baseline Characteristics								
Median time from baseline to breast cancer diagnosis (years)	6.0		6.7		7.1		6.9	
Age at baseline (mean±SD)	52.3±13.1		50.6±14.2		47.4±15.2		43.9±15.2	
Age at diagnosis (mean±SD)	63.1±12.6		60.6±12.8		57.6±13.0		53.6±12.3	
Age at menarche (mean±SD)	12.6±1.6		12.7±1.6		12.9±1.6		13.0±1.6	
	n	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Breast Cancer Cases	55	8.8	202	6.7	258	6.1	103	6.0
Race and ethnicity								
Asian	9	1.4	113	3.7	238	5.6	181	10.6
Hispanic	92	14.7	496	16.3	625	14.7	189	11.1
non-Hispanic Black	57	9.1	297	9.8	361	8.5	75	4.4
non-Hispanic White	436	69.9	2035	67.1	2888	67.9	1202	70.5
Other[a]	30	4.8	90	3.0	122	2.9	56	3.3
Missing	0	0.0	3	0.1	17	0.4	3	0.2
Education								
High school graduation/GED or less	277	44.4	1181	38.9	1266	29.8	399	23.4
Vocational or technical school/some college or university	234	37.5	1032	34.0	1471	34.6	571	33.5
Bachelor’s degree or higher	110	17.6	814	26.8	1502	35.3	733	43.0
Missing	3	0.5	7	0.2	12	0.3	3	0.2
Smoking status								
Never	238	38.1	1645	54.2	2660	62.6	1284	75.3
Former	246	39.4	901	29.7	1066	25.1	303	17.8
Current	137	22.0	477	15.7	516	12.1	111	6.5
Missing	3	0.5	11	0.4	9	0.2	8	0.5
Breastfed child for at least 1 month or longer								
No	276	44.2	1304	43.0	2038	47.9	828	48.5
Yes	342	54.8	1707	56.3	2188	51.5	865	50.7
Missing	6	1.0	23	0.8	25	0.6	13	0.8
Oral contraceptive use								
Never	157	25.2	887	29.2	1242	29.2	548	32.1
Ever	467	74.8	2138	70.5	2995	70.5	1155	67.7
Missing	0	0.0	9	0.3	14	0.3	3	0.2

	Adherence Score (n=9,615)							
	0 (n=624)		1 (n=3,034)		2 (n=4,251)		3 (n=1,706)	
	6.5%		31.6%		44.2%		17.7%	
Menopausal hormone use								
Never	400	64.1	2119	69.8	3124	73.5	1331	78.0
Ever	219	35.1	883	29.1	1080	25.4	357	20.9
Missing	5	0.8	32	1.1	47	1.1	18	1.1
Number of live births								
None	88	14.1	554	18.3	1081	25.4	511	30.0
1–2	241	38.6	1194	39.4	1611	37.9	658	38.6
3+	295	47.3	1284	42.3	1559	36.7	536	31.4
Missing	0	0.0	2	0.1	0	0.0	1	0.1
*BRCA*1/2 pathogenic variant status								
BRCA1/2 Negative[b]	612	98.1	2910	95.9	3981	93.6	1527	89.5
BRCA1/2 Positive	12	1.9	124	4.1	270	6.4	179	10.5

Abbreviations: BMI, body mass index; ACS, American Cancer Society; SD, standard deviation; GED, general educational development; *BRCA*, breast cancer gene.

[a.] The race and ethnicity category “other” was created based on self-reported “American Indian, Aleutian, or Eskimo” or “other” groups.

[b.] This group included women tested and not tested for *BRCA1/2* pathogenic variants. *BRCA1/2* testing was typically done on the youngest affected family member and if a *BRCA1/2* pathogenic variant was found, then family members were tested; therefore, women not tested are assumed negative.

Table 2:

Hazard ratios and 95% confidence intervals for the association between adherence to the American Cancer Society Guideline for Cancer Prevention recommendations on weight, physical activity, and alcohol consumption and risk of breast cancer for women in the Breast Cancer Family Registry

			Model 1[a]				Model 2[b]		
			BC events = 618 person-years=112,180.0				BC events = 618 person-years=112,180.0		
Binary	**BC**	**Person-years**	**HR**	**95% CI**	**p-value**		**HR**	**95% CI**	**p-value**
Adherent on none of the recommendations	55	7157.2	1.00	ref			1.00	ref	
Adherent on any of the recommendations	563	105022.9	0.77	(0.58–1.02)			0.73	(0.55–0.97)	
ACS Adherence Score									
Adherent on none of the recommendations	55	7157.2	1.00	ref			1.00	ref	
Adherent on 1 recommendation	202	34926.1	0.78	(0.58–1.06)			0.76	(0.56–1.03)	
Adherent on 2 recommendations	258	49614.0	0.75	(0.56–1.01)			0.71	(0.53–0.96)	
Adherent on 3 recommendations	103	20482.8	0.78	(0.56–1.09)			0.73	(0.52–1.02)	
p for trend					0.27				0.12

Abbreviations: BC, Breast Cancer; HR, hazard ratio; CI, confidence interval; GED, general education degree; OC, oral contraceptive; MHT, menopausal hormone therapy

[a] Model 1 is stratified by birth cohort (<1950, 1950–1959, 1960–1969, ≥1970)

[b] Model 2 is stratified by birth cohort (<1950, 1950–1959, 1960–1969, ≥1970) and adjusted for race and ethnicity (Asian, Hispanic, non-Hispanic Black, non-Hispanic White, other), education (less than high school graduation/GED, vocational or technical school/some college or university, Bachelor's degree or graduate school), cigarette use (never, former, current), OC use (never, ever), MHT use (never, ever), parity (none, 1–2 live births, 3+ live births), breastfeeding (never, ever), and age at menarche (continuous)

Note: Age was used as the underlying time scale

Table 3:

Hazard ratios and 95% confidence intervals for the association between adherence to the American Cancer Society Guideline for Cancer Prevention recommendations on weight, physical activity, and alcohol consumption and risk of breast cancer stratified by *BRCA1/2* pathogenic variant status, first-degree family history of breast cancer, and menopausal status for women in the Breast Cancer Family Registry

	***BRCA1/2* Negative[a]**							***BRCA1/2* Positive[b]**						
	BC events = 535 person-years=106,701.5							**BC events = 83 person-years=5,478.5**						
			Model 1[e]			**Model 2[f]**				**Model 1[e]**			**Model 2[f]**	
	BC	**Person-years**	**HR**	**95% CI**		**HR**	**95% CI**	**BC**	**Person-years**	**HR**	**95% CI**		**HR**	**95% CI**
Adherent on none of the recommendations	52	7067.9	1.00	ref		1.00	ref	3	89.3	1.00	ref		1.00	ref
Adherent on any of the recommendations	483	99633.6	0.74	(0.55–0.99)		0.71	(0.53–0.95)	80	5389.2	0.40	(0.13–1.17)		0.43	(0.16–1.20)
	No family history[c]							**Family history[c]**						
	BC events = 100 person-years=21,181.2							**BC events = 230 person-years=90,998.8**						
			Model 1[e]			**Model 2[f]**				**Model 1[e]**			**Model 2[f]**	
	BC	**Person-years**	**HR**	**95% CI**		**HR**	**95% CI**	**BC**	**Person-years**	**HR**	**95% CI**		**HR**	**95% CI**
Adherent on none of the recommendations	5	1280.1	1.00	ref		1.00	ref	50	5877.1	1.00	ref		1.00	ref
Adherent on any of the recommendations	95	19901.1	1.40	(0.57–3.47)		1.21	(0.47–3.09)	468	85121.8	0.71	(0.53–0.96)		0.68	(0.50–0.93)
	Premenopausal[d]							**Postmenopausal[d]**						
	BC events = 315 person-years=68,342.7							**BC events = 303 person-years=43,837.4**						
			Model 1[e]			**Model 2[f]**				**Model 1[e]**			**Model 2[f]**	
	BC	**Person-years**	**HR**	**95% CI**		**HR**	**95% CI**	**BC**	**Person-years**	**HR**	**95% CI**		**HR**	**95% CI**
Adherent on none of the recommendations	17	3294.5	1.00	ref		1.00	ref	38	3862.7	1.00	ref		1.00	ref
Adherent on any of the recommendations	298	65048.2	0.98	(0.60–1.60)		0.92	(0.56–1.50)	265	39974.7	0.66	(0.47–0.93)		0.63	(0.44–0.89)

Abbreviations: *BRCA*, breast cancer gene; BC, Breast Cancer; HR, hazard ratio; CI, confidence interval; GED, general education degree; OC, oral contraceptive; MHT, menopausal hormone therapy

[a] *BRCA1/2* negative defined as no *BRCA1* or *BRCA2* pathogenic variants or not tested. *BRCA1/2* testing was typically done on the youngest affected family member and if a *BRCA1/2* pathogenic variant was found, then family members were tested; therefore, women not tested are assumed negative.

[b] *BRCA1/2* positive defined as known *BRCA1* or *BRCA2* pathogenic variants

[c] Family history defined as having one or more first-degree relatives with breast cancer

[d] Participants missing menopausal status and imputed the data based on the 90th percentile of age at natural menopause for smokers and non-smokers (age 55 years for both).

[e] Model 1 is stratified by birth cohort (<1950, 1950–1959, 1960–1969, ≥1970)

[f] Model 2 is stratified by birth cohort (<1950, 1950–1959, 1960–1969, ≥1970) and adjusted for race and ethnicity (Asian, Hispanic, non-Hispanic Black, non-Hispanic White, other), education (less than high school graduation/GED, vocational or technical school/some college or university, Bachelor's degree or graduate school), cigarette use (never, former, current), OC use (never, ever), MHT use (never, ever), parity (none, 1–2 live births, 3+ live births), breastfed (never, ever), and age at menarche (continuous)

Note: Age was used as the underlying time scale. No multiplicative (p=0.33) or additive (RERI=−2.46, 95% CI: −11.19–6.27) interaction for *BRCA1/2* pathogenic variant status. No multiplicative (p=0.22) or additive (RERI=−0.94, 95% CI: −2.80, 0.91) interaction for first-degree family history of breast cancer. No multiplicative (p=0.17) or additive (RERI=−0.37, 95% CI: −1.10, 0.37) interaction for menopausal status.

Table 4:

Hazard ratios and 95% confidence intervals for the association between adherence to the American Cancer Society Guideline for Cancer Prevention recommendations on weight, physical activity, and alcohol consumption and risk of estrogen receptor-positive (ER+) breast cancer for women in the Breast Cancer Family Registry

			Model 1[a]			Model 2[b]	
			BC events = 230 person-years=109,171.9			BC events = 230 person-years=109,171.9	
	BC	Person-years	HR	95% CI		HR	95% CI
Adherent on none of the recommendations	23	6897.8	1.00	ref		1.00	ref
Adherent on any of the recommendations	207	102274.1	0.69	(0.45–1.08)		0.63	(0.40–0.98)

Abbreviations: BC, Breast Cancer; HR, hazard ratio; CI, confidence interval; GED, general education degree; OC, oral contraceptive; MHT, menopausal hormone therapy

[a] Model 1 is stratified by birth cohort (<1950, 1950–1959, 1960–1969, ≥1970)

[b] Model 2 is stratified by birth cohort (<1950, 1950–1959, 1960–1969, ≥1970) and adjusted for race and ethnicity (Asian, Hispanic, non-Hispanic Black, non-Hispanic White, other), education (less than high school graduation/GED, vocational or technical school/some college or university, Bachelor's degree or graduate school), cigarette use (never, former, current), OC use (never, ever), MHT use (never, ever), parity (none, 1–2 live births, 3+ live births), breastfeeding (never, ever), and age at menarche (continuous)

Note: Age was used as the underlying time scale.