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Testing for Gene-Environment Interactions Using a Prospective Family Cohort Design: Body Mass Index in Early and Later Adulthood and Risk of Breast Cancer

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The ability to classify people according to their underlying genetic susceptibility to a disease is increasing with new knowledge, better family data, and more sophisticated risk prediction models, allowing for more effective prevention and screening. To do so, however, we need to know whether risk associations are the same for people with different genetic susceptibilities. To illustrate one way to estimate such gene-environment interactions, we used prospective data from 3 Australian family cancer cohort studies, 2 enriched for familial risk of breast cancer. There were 288 incident breast cancers in 9,126 participants from 3,222 families. We used Cox proportional hazards models to investigate whether associations of breast cancer with body mass index (BMI; weight (kg)/height $(m)^2$) at age 18–21 years, BMI at baseline, and change in BMI differed according to genetic risk based on lifetime breast cancer risk from birth, as estimated by BOADICEA (Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm) software, adjusted for age at baseline data collection. Although no interactions were statistically significant, we have demonstrated the power with which gene-environment interactions can be investigated using a cohort enriched for persons with increased genetic risk and a continuous measure of genetic risk based on family history.

BOADICEA; body mass index; breast cancer; cohort studies; familial risk; family studies; gene-environment interaction

Abbreviations: ABCFR, Australian Breast Cancer Family Registry; ACCFR, Australian Colorectal Cancer Family Registry; BMI, body mass index; BOADICEA, Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm; *BRCA1*, breast cancer 1, early-onset gene; *BRCA2*, breast cancer 2, early-onset gene; CI, confidence interval; kConFab, Kathleen Cuningham Foundation Consortium for Research into Familial Breast Cancer; SD, standard deviation; SNP, single-nucleotide polymorphism; *TP53*, tumor protein p53 gene.

The ability to classify people according to their underlying genetic susceptibility to a specific disease is increasing with new knowledge on genetic risk factors, better family data, and more sophisticated risk prediction models. This opens up the potential for more effective prevention and screening. To do so, however, we need to know whether risk associations are the same for people with different genetic susceptibilities.

Taking breast cancer as an example, current information from mutation screening (1) and multiple markers of genetic susceptibility (including single-nucleotide polymorphisms (SNPs)) (2), especially when combined with multigenerational family cancer history (3), can be used to develop risk prediction scores with an interquartile risk ratio of 5 or more (3). The cost of measuring genetic markers is decreasing, and classification of risk is likely to improve through the use of genetic risk scores that are based on more markers, and perhaps by using alternative approaches to the usual statistical significance of individual markers to choose them.

The Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm (BOADICEA) (http://ccge.medschl.cam.ac.uk/boadicea/) estimates genetic risk of breast and ovarian cancer by modeling major genes and

polygenes (3–5). BOADICEA has been shown to be well calibrated and to have good discriminatory accuracy for Australian women (6). BOADICEA is being extended to include more measured genetic and environmental or lifestyle risk factors, including mammographic density (7, 8).

A woman's risk of breast cancer depends on both her underlying genetic predisposition and some environmental and lifestyle factors she experiences during her lifetime. Few epidemiologic studies of breast cancer have measured both genetic and nongenetic risk factors comprehensively, and fewer have addressed gene-environment interactions by using global measures of genetic risk based on complex models of multigenerational family data (as distinct from considering individual measured genetic markers of risk). Moreover, previous studies of gene-environment interactions have not used samples enriched for familial risk, which limits statistical power to detect differences across the full spectrum of risk (9).

Environmental and lifestyle risk factor associations could be stronger or weaker for women at higher genetic risk of breast cancer than for women at a lower genetic risk. Such gene-environment interactions could result in substantial gradients in absolute risk for women at increased genetic risk of breast cancer and make it possible to better identify women at high risk who might benefit from additional screening or preventive measures appropriate for their risk. Finding gene-environment interactions could also show that some risk factors for women in the general population do not apply to women at high genetic risk. On the other hand, a lack of evidence for a gene-environment interaction from studies with sufficient power would mean that a modifiable risk factor for women in the general population, who are mostly at very low risk, is also important for women at the higher end of genetic risk. Either way, clarification of the issue of gene-environment interactions is important.

To illustrate one way to find evidence for gene-environment interactions, we used 3 prospective family cohorts enriched for familial risk (10) to investigate whether associations between breast cancer risk and body mass index (BMI) differ according to a woman's underlying genetic risk of breast cancer. We chose BOADICEA to estimate genetic risk because, being founded on likelihood theory, it makes optimal use of family data and can be continually updated to include new risk information, such as genetic risk scores based on SNPs. We chose BMI because it is an example of a potentially modifiable continuous risk factor for which we had 2 correlated measurements: one taken in early adulthood and one in later life. Using this example, we considered the issue of multiple risk factors and allowed for the possibility that the interactions can differ. We chose to fit multiplicative interactions to demonstrate our approach because they are standard, appreciating that other models such as those including data from SNPs could have been fitted.

METHODS

Subjects

We studied women who were unaffected by invasive breast cancer at enrollment in 3 large Australian family cancer cohort studies: the Australian Breast Cancer Family Registry (ABCFR), the Kathleen Cuningham Foundation Consortium for Research into Familial Breast Cancer (kConFab), and the Australasian Colorectal Cancer Family Registry (ACCFR).

Australian Breast Cancer Family Registry. From 1992 to 1999, probands and their relatives were recruited into the ABCFR as described previously (11–16). Briefly, probands included population-based cases who were aged less than 60 years when diagnosed with an incident first primary invasive breast cancer (identified through population-complete cancer registries); population-based controls aged less than 60 years at recruitment (identified through the electoral roll, for which registration is mandatory for Australian adults); Ashkenazi Jewish women with a family history of breast cancer; and twin pairs (identified through the Australian Twin Registry) in which one or both twins had breast cancer. Living adult first-degree relatives, aunts, and grandparents were invited to participate, and additional recruitment occurred iteratively; if identified relatives had a diagnosis of breast cancer, participation was sought from them and their first-degree relatives (13, 14).

At baseline, all participants completed an interviewer-administered risk factor questionnaire that asked about their demographic background, personal characteristics, reproductive history, environmental risk factors, lifestyle risk factors, surgeries, and personal history of breast and other cancers (12, 14). Participants were also asked to provide cancer history information on all of their first-degree and second-degree relatives (12, 14). This ensured that cancer information was obtained from multiple sources and that, for each individual, cancer history was usually self-reported or reported by a first-degree relative. Verification of cancers was sought through pathologist reviews of cancer tissue, pathology reports, cancer registries, medical records, and death certificates (12, 14).

Participants were recontacted approximately 10 years and 15 years after their baseline interview and invited to take part in the follow-up phase of the ABCFR. The follow-up questionnaires were either interviewer-administered during a telephone interview or self-administered with a telephone interview used to obtain additional details if required. The follow-up questionnaires updated the data collected in the baseline questionnaire, and participants were also asked to provide an updated cancer history for their first- and second-degree relatives and the date(s) of death for any deceased relatives. Where possible, reports of new cancer diagnoses were verified using pathology reports and medical records.

Ethics approval for the ABCFR was obtained from the human research ethics committees of the University of Melbourne and the Cancer Councils of Victoria and New South Wales. All participants provided written informed consent before taking part in the research.

Kathleen Cuningham Foundation Consortium for Research into Familial Breast Cancer. Starting in 1997, families with multiple cases of breast cancer were recruited into kConFab as described previously (17). Briefly, eligible families were identified from women undergoing clinical consultations at 24 family cancer clinics in Australia and New Zealand. Eligible families included those with a strong family history of breast or ovarian cancer or a confirmed mutation in the breast cancer 1,

early-onset gene (*BRCA1*) or the breast cancer 2, early-onset gene (*BRCA2*) (18). At baseline, participants provided a blood sample for genetic analyses and completed the questionnaire used by the ABCFR (14).

Every 3 years, all female participants are invited to participate in the kConFab follow-up study, as described in detail previously (19). In kConFab follow-up, a mailed self-administered questionnaire is used to systematically update the baseline questionnaire data and information on personal cancer history, family cancer history, environmental risk factors, lifestyle risk factors, and uptake of cancer prevention and screening strategies. When possible, self-reports of new cancer diagnoses and prophylactic surgeries were verified using pathology reports and medical records.

Ethics approval for kConFab was obtained from the coordinating site at the Peter MacCallum Cancer Centre (Melbourne, Victoria, Australia) and from each of its recruitment sites. All participants provided written informed consent before taking part in the research.

Australasian Colorectal Cancer Family Registry. From 1998 to 2007, families were recruited into the ACCFR for a study of the genetic, environmental, and lifestyle factors associated with colorectal cancer, as described previously (20, 21). In brief, probands included men and women who were aged less than 60 years when diagnosed with incident first primary invasive colorectal cancer (identified from the population-complete Victorian Cancer Registry) and affected and unaffected individuals with a family history of colorectal cancer or related cancers who were recruited from family cancer clinics in Australia and New Zealand.

For all probands, their living adult first- and second-degree relatives were invited to participate. If an identified relative had a diagnosis of colorectal cancer or a related cancer, participation was sought from that person and his or her first-degree relatives.

At baseline, all participants completed a questionnaire that asked about their demographic background, personal characteristics, medical history, medication use, reproductive history (for females), physical activity, diet, smoking, alcohol use, and personal history of cancer (20). The questionnaire used by the ACCFR (22) was based on the questionnaire used by the ABCFR and kConFab. Participants were also asked to provide information on the cancer histories of all of their first- and second-degree relatives so that cancer history information was obtained from multiple sources. Verification of cancers was sought through pathology reports, medical records, cancer registries, and death certificates (20).

Participants have been followed up approximately every 5 years and asked to complete a self-administered questionnaire to update data on the information collected at baseline and to provide updated cancer histories for their first- and second-degree relatives (21, 23). Where possible, reports of new cancer diagnoses were verified using pathology reports and medical records.

Ethics approval for the ACCFR was granted by the Human Research Ethics Committee at the University of Melbourne.

Eligibility. For the present study, female ABCFR and kConFab participants were eligible if they had not been diagnosed with invasive breast cancer at baseline; they had not had a mastectomy (unilateral or bilateral) before baseline; they had not had an oophorectomy (unilateral or bilateral) before baseline; they and their family had no deleterious mutations in *BRCA1*, *BRCA2*, or the tumor protein p53 gene (*TP53*); and they had completed a baseline questionnaire and provided data for all of the height and weight questions. ABCFR participants were included if at least 1 member of their family had completed a follow-up questionnaire, while the kConFab participants were included if they had completed at least 1 follow-up questionnaire.

Female ACCFR participants were eligible if they had not been diagnosed with invasive breast cancer at baseline; they had completed a baseline questionnaire and provided valid data for the height and weight questions; and at least 1 member of their family had completed a follow-up questionnaire. It was not possible to exclude women who had had a mastectomy or oophorectomy before baseline because this information was not collected. The ACCFR did not test for mutations in *BRCA1*, *BRCA2*, or *TP53*.

Statistical analysis

On the baseline risk factor questionnaires that were completed at enrollment in the cohorts, participants were asked about their height, their current weight, and their weight when they were aged 18–21 years (or aged 20 years for the ACCFR). BMI at baseline and BMI at ages 18–21 years were calculated as current weight (kg) and weight at ages 18–21 years (kg), respectively, divided by the square of height (m^2) at baseline. Because there were so few missing values for the other risk factor questions used in analyses—1 for smoking and 19 for use of hormone replacement therapy—these persons were taken to be nonsmokers and nonusers, respectively.

We considered each BMI measure separately and then together. We calculated change in BMI (from ages 18–21 years to baseline data collection) as the difference between the 2 BMI measures, and we fitted that measure alone and then combined with one or other of the 2 other measures. Note that knowing any 2 of the BMI measures defines the third.

For each eligible participant, we estimated genetic risk using BOADICEA to calculate the person's lifetime risk (from birth) of invasive breast cancer (4, 5) using baseline pedigree information from all participating and nonparticipating family members and Australian cancer incidence rates (6). To ensure that BOADICEA lifetime risk scores could be calculated for all eligible participants, missing pedigree data were imputed using a previously developed protocol (14, 24). We adjusted BOADICEA lifetime risk score for baseline age as a quadratic function because we wanted to compare women of the same age, and as a woman gets older, her living relatives also get older and her cancer family history becomes more informative.

Time in the study began at the date of the baseline interview and ended at whichever of the following came first: the last follow-up questionnaire, diagnosis of invasive breast cancer, death, mastectomy, oophorectomy, or age 80 years.

We fitted Cox proportional hazards models using age as the time axis and stratifying by age at interview in 2-year

groups to estimate hazard ratios for the risk of invasive breast cancer. Because our eligible participants included families with multiple members, we calculated robust estimates of confidence intervals by clustering by family. Tests of the proportional hazards assumption were based on Schoenfeld residuals.

We tested for evidence of multiplicative gene-environment interactions using interaction terms created by multiplying each BMI measure by the BOADICEA lifetime risk score, adjusted for a quadratic function of age at baseline data collection. We then included one or both of these interaction terms in the models.

Stata, version 13 (StataCorp LP, College Station, Texas) was used for all statistical analyses (25). All statistical tests were 2-sided, and P values less than 0.05 were considered nominally statistically significant.

RESULTS

We studied 9,126 participants from 3,222 families. On average, participants were aged 45.9 years (standard deviation (SD), 15.0) at baseline and contributed 10.0 years (SD, 4.1) of follow-up time, during which 288 invasive breast cancers were diagnosed at a mean age of 56.6 years (SD, 12.3). Table 1 provides more detail on the cohort.

Table 2 shows the distributions, unadjusted hazard ratios (and 95% confidence intervals), and P values for the participants' baseline BOADICEA lifetime risk scores, BMI measures, and risk factor questions. For the risk factors originally measured on a continuous scale, the mean values were: 13.2% (SD, 5.5) for BOADICEA lifetime risk; 21.5 (SD, 3.6) for BMI at ages 18–21 years; 25.2 (SD, 5.4) for BMI at baseline; 3.6 (SD, 4.6) for change in BMI since ages 18–21 years; 13.0 years (SD, 1.5) for age at menarche; and 2.0 (SD, 1.7) for number of live births.

Breast cancer risk increased with unadjusted BOADICEA lifetime risk score and with having a first-degree relative with breast cancer (Table 2). The hazard ratios for the continuous measurements were: 1.24 (95% confidence interval (CI): 1.14, 1.35; $P < 0.001$) for each 5% increment in BOADICEA lifetime risk; 1.07 (95% CI: 0.97, 1.19; $P = 0.2$) for each 5-unit increment in BMI at baseline; 0.94 (95% CI: 0.79, 1.12; $P = 0.5$) for each 5-unit increment in BMI at ages 18–21 years; 1.13 (95% CI: 1.02, 1.26; $P = 0.02$) for each 5-unit change in BMI since ages 18–21 years; 0.97 (95% CI: 0.91, 1.05; $P = 0.5$) for each year of age at menarche; and 1.00 (95% CI: 0.92, 1.08; $P = 1.0$) for each live birth. We also fitted models that allowed the BMI associations to depend on age at baseline but did not find any statistically significant effect modifications (data not shown).

Table 1. Characteristics of Families, Participants, and Breast Cancers in 3 Australian Family Cancer Cohorts (ABCFR, kConFab, and ACCFR), by Source of Proband, 1992–2010

Source of Proband	No. of Families	No. of Participants	Mean (SD) No. of Participants per Family	Mean (SD) Age at Baseline, years	Mean (SD) Duration of Follow-up, years	No. of Breast Cancers	Mean (SD) Age at Diagnosis, years
ABCFR							
Cases by age group, years							
<40	418	1,168	2.8 (1.9)	50.7 (14.9)	14.1 (3.5)	64	62.7 (11.8)
40–49	254	571	2.2 (1.4)	47.3 (17.6)	13.6 (3.0)	31	58.0 (13.6)
50–59	225	556	2.5 (1.5)	43.2 (16.8)	14.0 (2.7)	20	57.9 (12.5)
Population controls							
Age group, years							
<40	157	433	2.8 (1.6)	44.2 (14.5)	12.3 (1.9)	12	51.9 (12.2)
40–49	154	359	2.3 (1.2)	45.6 (13.5)	11.7 (1.9)	9	58.6 (10.7)
50–59	167	401	2.4 (1.5)	46.3 (14.8)	12.1 (2.0)	10	61.3 (10.1)
Twins	14	53	3.8 (2.4)	45.2 (15.1)	13.2 (2.2)	2	44.5 (4.9)
Ashkenazi Jews	56	64	1.1 (0.4)	43.9 (11.4)	15.2 (2.0)	4	54.0 (9.8)
kConFab	637	1,925	3.0 (2.2)	44.6 (14.6)	7.1 (3.3)	80	52.0 (11.3)
ACCFR							
Cases by age group, years							
<45	246	566	2.3 (1.5)	43.9 (14.8)	8.0 (2.9)	8	52.4 (12.5)
45–59	437	1,141	2.6 (1.7)	45.7 (14.5)	8.9 (2.5)	25	56.3 (11.1)
Clinic-based	457	1,889	4.1 (3.4)	45.8 (14.2)	7.8 (3.0)	23	55.4 (12.3)
Total	3,222	9,126	2.8 (2.2)	45.9 (15.0)	10.0 (4.1)	288	56.6 (12.3)

Abbreviations: ABCFR, Australian Breast Cancer Family Registry; ACCFR, Australasian Colorectal Cancer Family Registry; kConFab, Kathleen Cuningham Foundation Consortium for Research into Familial Breast Cancer; SD, standard deviation.

Table 2. Distributions of BOADICEA Risk Scores, Body Mass Index Measures, and Responses to Risk Factor Questions in 3 Australian Family Cancer Cohorts (ABCFR, kConFab, and ACCFR) and Unadjusted Hazard Ratios for Breast Cancer According to Those Factors, 1992–2010

Risk Factor	No. of Participants	%	Risk of Breast Cancer		
			HR	95% CI	*P* Value
BOADICEA lifetime risk score[a], %					
Q1 (0.29–9.51)	2,228	24.4	1	Referent	
Q2 (9.52–11.03)	2,301	25.2	1.01	0.65, 1.58	1.0
Q3 (11.04–16.27)	2,287	25.1	1.81	1.27, 2.58	0.001
Q4 (16.28–59.09)	2,310	25.3	2.16	1.52, 3.06	<0.001
BMI[b] at ages 18–21 years[c]					
Q1 (11.34–19.15)	2,181	23.9	1	Referent	1
Q2 (19.16–20.93)	2,382	26.1	1.03	0.75, 1.42	0.8
Q3 (20.94–23.06)	2,280	25.0	0.89	0.64, 1.25	0.5
Q4 (23.07–68.69)	2,283	25.0	0.92	0.66, 1.30	0.7
BMI at baseline[d]					
Q1 (11.72–21.45)	2,230	24.4	1	Referent	1
Q2 (21.46–24.02)	2,324	25.5	1.18	0.84, 1.66	0.3
Q3 (24.03–27.68)	2,276	24.9	1.34	0.94, 1.91	0.1
Q4 (27.69–65.75)	2,296	25.2	1.26	0.88, 1.81	0.2
Change in BMI[e]					
Q1 (−45.18 to 0.39)	2,281	25.0	1	Referent	1
Q2 (0.40–2.71)	2,380	25.0	1.16	0.78, 1.72	0.5
Q3 (2.72–5.86)	2,270	24.9	1.56	1.09, 2.24	0.02
Q4 (5.87–40.40)	2,295	25.1	1.52	1.05, 2.19	0.03
Country of birth					
Australia	7,430	81.4	1	Referent	
Overseas	1,693	18.6	0.79	0.59, 1.07	0.1
Missing data	3	0.0			
Highest level of education completed					
Year 10	1,908	20.9	1	Referent	
Year 11–12 or vocational training	4,216	46.2	0.91	0.66, 1.26	0.6
University degree	2,981	32.7	0.90	0.64, 1.27	0.5
Missing data	21	0.2			
Marital status					
Never married	1,365	15.0	1	Referent	
Married or living as married	7,748	84.9	1.28	0.75, 2.17	0.4
Missing data	13	0.1			
Age at menarche, years					
<12	1,389	15.2	1	Referent	
12	1,931	21.2	1.03	0.71, 1.49	0.9
13	2,522	27.6	0.98	0.69, 1.40	0.9
14	1,762	19.3	1.03	0.71, 1.49	0.9
≥15	1,470	16.1	0.77	0.50, 1.17	0.2
Missing data	52	0.6			
Ever having been pregnant					
No	1,865	20.4	1	Referent	
Yes	7,261	79.6	1.11	0.75, 1.63	0.6
Ever having a live birth					
No	2,267	24.8	1	Referent	
Yes	6,859	75.2	1.10	0.76, 1.58	0.6

Table continues

Table 2. Continued

Risk Factor	No. of Participants	%	Risk of Breast Cancer		
			HR	95% CI	*P* Value
No. of live births					
0	2,267	24.8	1	Referent	
1	946	10.4	1.19	0.73, 1.91	0.5
2	2,499	27.4	1.10	0.73, 1.65	0.6
3	1,966	21.5	1.13	0.75, 1.70	0.6
≥4	1,447	15.9	0.95	0.60, 1.50	0.8
Missing data	1	0.0			
Ever use of oral contraceptives					
No	1,931	21.2	1	Referent	
Yes	7,192	78.8			
Missing data	3	0.0	1.06	0.77, 1.45	0.7
Menopause					
No	5,465	59.9	1	Referent	
Yes	3,661	40.1	0.71	0.41, 1.24	0.2
Ever use of hormone replacement therapy					
No	7,333	80.4	1	Referent	
Yes	1,774	19.4	1.33	0.99, 1.77	0.05
Missing data	19	0.2			
Breast cancer in a first-degree relative					
No	5,267	57.7	1	Referent	
Yes	3,859	42.3	1.95	1.52, 2.50	<0.001
Smoking					
Never smoker	4,968	54.4	1	Referent	
Past smoker	2,557	28.0	1.08	0.83, 1.39	0.6
Current smoker	1,600	17.5	0.68	0.46, 1.00	0.05
Missing data	1	0.0			
Ever drinking alcohol					
No	3,626	39.7	1	Referent	
Yes	5,496	60.2	0.95	0.75, 1.20	0.7
Missing data	4	0.0			

Abbreviations: ABCFR, Australian Breast Cancer Family Registry; ACCFR, Australasian Colorectal Cancer Family Registry; BMI, body mass index; BOADICEA, Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm; CI, confidence interval; HR, hazard ratio; kConFab, Kathleen Cuningham Foundation Consortium for Research into Familial Breast Cancer; Q, quartile.

[a] BOADICEA risk score was divided into quartiles with the following median values: Q1, 9.09%; Q2, 9.86%; Q3, 13.74%; and Q4, 18.74%.

[b] Weight (kg)/height $(m)^2$.

[c] BMI at ages 18–21 years was divided into quartiles with the following median values: Q1, 18.25; Q2, 20.20; Q3, 21.91; and Q4, 24.91.

[d] BMI at baseline was divided into quartiles with the following median values: Q1, 19.95; Q2, 22.66; Q3, 25.56; and Q4, 31.17.

[e] Change in BMI was divided into quartiles with the following median values: Q1, 0.00; Q2, 1.63; Q3, 4.06; and Q4, 8.65.

Table 3 shows the fits for combinations of the BMI measures, age-adjusted BOADICEA risk score, and their multiplicative interactions. Models 1–3 show that the only BMI measure associated with risk on its own was change in BMI from ages 18–21 years to baseline ($P = 0.03$). Model 4 shows that age-adjusted BOADICEA score was strongly associated with breast cancer risk ($P < 0.001$), and comparison with models 5–7 shows that this association did not change after adjusting for the BMI measures one at a time. Similarly, comparisons of models 5–7 with models 1–3 show

Table 3. Adjusted Hazard Ratios for Breast Cancer According to Body Mass Index and BOADICEA Risk Score in 3 Australian Family Cancer Cohorts (ABCFR, kConFab, and ACCFR), 1992–2010

Model and Adjustment Criteria	Risk of Breast Cancer			
	HR[a]	95% CI	*P* Value	Δ LL[b]
Model 1				0.17
BMI[c] at ages 18–21 years (per 5-unit increment)	0.95	0.80, 1.13	0.5	
Model 2				0.77
BMI at baseline (per 5-unit increment)	1.07	0.97, 1.19	0.2	
Model 3				1.70
BMI change[d] (per 5-unit increment)	1.13	1.01, 1.25	0.03	
Model 4				9.61
BOADICEA risk score[e] (per 5% increment)	1.24	1.14, 1.35	<0.001	
Model 5				9.76
BMI at ages 18–21 years	0.95	0.80, 1.13	0.6	
BOADICEA risk score	1.24	1.14, 1.35	<0.001	
Model 6				10.57
BMI at baseline	1.08	0.98, 1.20	0.1	
BOADICEA risk score	1.25	1.15, 1.36	<0.001	
Model 7				11.59
BMI change	1.14	1.02, 1.27	0.02	
BOADICEA risk score	1.25	1.15, 1.36	<0.001	
Model 8				10.40
BMI at ages 18–21 years	1.02	0.85, 1.24	0.8	
BOADICEA risk score	1.79	0.94, 3.43	0.08	
BMI at 18–21 years × BOADICEA score	0.92	0.78, 1.07	0.3	
Model 9				11.50
BMI at baseline	1.14	1.01, 1.28	0.03	
BOADICEA risk score	1.70	1.12, 2.57	0.01	
BMI at baseline × BOADICEA score	0.94	0.87, 1.02	0.1	
Model 10				11.83
BMI change	1.17	1.03, 1.33	0.02	
BOADICEA risk score	1.28	1.16, 1.42	<0.001	
BMI change × BOADICEA score	0.97	0.90, 1.04	0.4	
Model 11				11.64
BMI at ages 18–21 years	0.86	0.71, 1.03	0.1	
BMI at baseline	1.14	1.02, 1.27	0.03	
BOADICEA risk score	1.25	1.15, 1.36	<0.001	
Model 12				11.64
BMI at ages 18–21 years	0.97	0.82, 1.16	0.8	
BMI change	1.14	1.02, 1.27	0.03	
BOADICEA risk score	1.25	1.15, 1.36	<0.001	
Model 13				11.64
BMI at baseline	0.97	0.82, 1.16	0.8	
BMI change	1.17	0.97, 1.40	0.1	
BOADICEA risk score	1.25	1.15, 1.36	<0.001	
Model 14				12.69
BMI at ages 18–21 years	0.90	0.73, 1.12	0.3	
BMI at baseline	1.18	1.04, 1.34	0.01	
BOADICEA risk score	1.97	0.98, 3.96	0.06	

Table continues

Table 3. Continued

Model and Adjustment Criteria	Risk of Breast Cancer			
	HR[a]	95% CI	*P* Value	Δ LL[b]
BMI at 18–21 years × BOADICEA score	0.95	0.81, 1.11	0.5	
BMI at baseline × BOADICEA score	0.95	0.88, 1.04	0.3	
Model 15				12.69
BMI at ages 18–21 years	1.06	0.87, 1.30	0.6	
BMI change	1.18	1.04, 1.34	0.01	
BOADICEA risk score	1.97	0.98, 3.96	0.06	
BMI at 18–21 years × BOADICEA score	0.90	0.77, 1.06	0.2	
BMI change × BOADICEA score	0.95	0.88, 1.04	0.3	
Model 16				12.69
BMI at baseline	1.06	0.87, 1.30	0.6	
BMI change	1.11	0.90, 1.38	0.3	
BOADICEA risk score	1.97	0.98, 3.96	0.06	
BMI at baseline × BOADICEA score	0.90	0.77, 1.06	0.2	
BMI change × BOADICEA score	1.05	0.90, 1.23	0.5	

Abbreviations: ABCFR, Australian Breast Cancer Family Registry; ACCFR, Australasian Colorectal Cancer Family Registry; BMI, body mass index; BOADICEA, Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm; CI, confidence interval; HR, hazard ratio; kConFab, Kathleen Cuningham Foundation Consortium for Research into Familial Breast Cancer; LL, log-likelihood.

[a] Adjusted for smoking and use of hormone replacement therapy.

[b] Change in LL from the base model that included smoking and use of hormone replacement therapy.

[c] Weight (kg)/height $(m)^2$.

[d] Change in BMI from ages 18–21 years to baseline.

[e] Adjusted for baseline age and age^2.

that the BMI associations were unchanged after adjustment for age-adjusted BOADICEA score.

Models 8–10 show that there was no evidence for a multiplicative interaction between any of the BMI measures and age-adjusted BOADICEA score (all P values > 0.1).

Models 11–13 considered the pairs of BMI measures, and all 3 gave similar fits with the same associations with age-adjusted BOADICEA score. The associations with BMI at ages 18–21 years and BMI at baseline both diverged from the null when fitted together (model 11 compared with models 5 and 6). After adjustment for BMI at ages 18–21 years, both BMI at baseline and BMI change were associated with an increased risk of breast cancer (both P values $= 0.03$).

Models 14–16 considered the pairs of BMI measures, this time allowing for each measure to have a multiplicative interaction with age-adjusted BOADICEA score (all models gave similar fits). After adjustment for BMI at ages 18–21 years, both BMI at baseline and BMI change were associated with an increased risk of breast cancer ($P = 0.04$). The change in likelihood from models 11–13 to models 14–16 was not significant ($P = 0.4$).

We repeated the modeling shown in Table 3 after excluding women from the ACCFR who had colorectal cancer at baseline and found no change in the results (data not shown). We also repeated the modeling after stratifying by menopausal status (Table 4).

Figures 1 and 2 show the associations predicted by the 2 interaction models (models 14 and 15) that included BMI at ages 18–21 years. Log hazard ratio estimates for both BMI measures tended to decrease with increasing age-adjusted BOADICEA score. To illustrate interpretations, ignoring the lack of statistical evidence for multiplicative interactions, the predictions from these model fits would be: 1) for women in the lower quartiles of age-adjusted BOADICEA score, after taking into account BMI at ages 18–21 years, both BMI at baseline and change in BMI were associated with an increased risk of breast cancer; and 2) for women in the upper quartile of age-adjusted BOADICEA score, BMI at ages 18–21 years was associated with a decreased risk of breast cancer.

DISCUSSION

These analyses show how evidence for multiplicative gene-environment interactions can be assessed using family history data to predict underlying genetic risk. Nonmultiplicative interactions or interactions involving individual SNPs could have been similarly considered by changing the model parameterization. We age-adjusted lifetime risk estimated by BOADICEA score as a surrogate for genetic risk because the lifetime risk predicted from family history increases with age and because we compared risk factors for women of the same age.

Table 4. Adjusted Hazard Ratios for Breast Cancer According to Body Mass Index and BOADICEA Risk Score in 3 Australian Family Cancer Cohorts (ABCFR, kConFab, and ACCFR), by Menopausal Status, 1992–2010

Model and Adjustment Criteria	Risk of Breast Cancer							
	Premenopausal Women				Postmenopausal Women			
	HR[a]	95% CI	*P* Value	Δ LL[b]	HR[a]	95% CI	*P* Value	Δ LL[b]
Model 1				0.34				1.78
BMI[c] at ages 18–21 years (per 5-unit increment)	1.01	0.89, 1.36	0.4		0.76	0.58, 0.99	0.04	
Model 2				0.79				0.04
BMI at baseline (per 5-unit increment)	1.10	0.96, 1.26	0.2		1.03	0.88, 1.21	0.7	
Model 3				0.43				1.20
BMI change[d] (per 5-unit increment)	1.10	0.93, 1.29	0.3		1.14	0.99, 1.33	0.08	
Model 4				7.61				2.30
BOADICEA risk score[e] (per 5% increment)	1.27	0.16, 1.40	<0.001		1.20	1.03, 1.41	0.02	
Model 5				7.99				4.14
BMI at ages 18–21 years	1.11	0.90, 1.37	0.3		0.76	0.58, 0.98	0.04	
BOADICEA risk score	1.26	1.16, 1.40	<0.001		1.20	1.03, 1.40	0.02	
Model 6				8.64				2.38
BMI at baseline	1.11	0.97, 1.27	0.1		1.04	0.88, 1.22	0.7	
BOADICEA risk score	1.28	1.16, 1.41	<0.001		1.20	1.03, 1.41	0.02	
Model 7				8.24				3.64
BMI change	1.12	0.95, 1.31	0.2		1.15	0.99, 1.34	0.07	
BOADICEA risk score	1.28	1.16, 1.41	<0.001		1.21	1.03, 1.41	0.02	
Model 8				8.37				5.66
BMI at ages 18–21 years	1.12	0.94, 1.53	0.1		0.89	0.67, 1.18	0.4	
BOADICEA risk score	1.74	0.87, 3.47	0.1		3.66	1.40, 9.58	0.008	
BMI at 18–21 years × BOADICEA score	0.93	0.79, 1.09	0.4		0.76	0.60, 0.97	0.03	
Model 9				8.72				3.60
BMI at baseline	1.14	0.97, 1.35	0.1		1.12	0.94, 1.32	0.2	
BOADICEA risk score	1.44	0.88, 2.34	0.1		2.43	1.12, 5.27	0.03	
BMI × BOADICEA score	0.98	0.88, 1.08	0.6		0.87	0.75, 1.01	0.08	
Model 10				8.26				3.79
BMI change	1.10	0.91, 1.33	0.3		1.19	0.99, 1.43	0.07	
BOADICEA risk score	1.27	1.14, 1.41	<0.001		1.27	1.00, 1.62	0.05	
BMI change × BOADICEA score	1.02	0.91, 1.13	0.8		0.95	0.83, 1.10	0.5	
Model 11				8.64				4.91
BMI at ages 18–21 years	0.99	0.77, 1.28	1.0		0.70	0.53, 0.92	0.01	
BMI at baseline	1.12	0.96, 1.30	0.2		1.12	0.95, 1.32	0.2	
BOADICEA risk score	1.28	1.16, 1.41	<0.001		1.21	1.03, 1.41	0.02	
Model 12				8.64				4.91
BMI at ages 18–21 years	1.11	0.90, 1.37	0.3		0.79	0.60, 1.04	0.09	
BMI change	1.12	0.96,1.30	0.2		1.12	0.95, 1.32	0.2	
BOADICEA risk score	1.28	1.16,1.41	<0.001		1.21	1.03, 1.41	0.02	
Model 13				8.64				4.91
BMI at baseline	1.11	0.90, 1.37	0.3		0.79	0.60, 1.04	0.09	
BMI change	1.01	0.78, 1.29	1.0		1.42	1.08, 1.87	0.01	
BOADICEA risk score	1.28	1.16, 1.41	<0.001		1.21	1.03, 1.41	0.02	
Model 14				12.01				6.87
BMI at ages 18–21 years	1.08	0.83, 1.42	0.6		0.79	0.57, 1.10	0.2	
BMI at baseline	1.11	0.92, 1.33	0.3		1.17	0.97, 1.42	0.09	

Table continues

Table 4. Continued

Model and Adjustment Criteria	Risk of Breast Cancer							
	Premenopausal Women				Postmenopausal Women			
	HR[a]	95% CI	*P* Value	Δ LL[b]	HR[a]	95% CI	*P* Value	Δ LL[b]
BOADICEA risk score	1.72	0.83, 3.58	0.1		4.48	1.56, 12.90	0.005	
BMI at 18–21 years × BOADICEA score	0.92	0.87, 1.09	0.4		0.81	0.63, 1.05	0.1	
BMI at baseline × BOADICEA score	1.01	0.91, 1.12	0.9		0.91	0.78, 1.07	0.2	
Model 15				12.01				6.87
BMI at ages 18–21 years	1.20	0.94, 1.53	0.1		0.93	0.69, 1.25	0.6	
BMI change	1.11	0.92, 1.33	0.3		1.17	0.97, 1.42	0.09	
BOADICEA risk score	1.72	0.83, 3.58	0.1		4.48	1.56, 12.90	0.005	
BMI at 18–21 years × BOADICEA score	0.93	0.79, 1.01	0.4		0.74	0.58, 0.95	0.02	
BMI change × BOADICEA score	1.01	0.91, 1.23	0.9		0.91	0.78, 0.95	0.2	
Model 16				12.01				6.87
BMI at baseline	1.20	0.94, 1.53	0.1		0.93	0.69, 1.25	0.6	
BMI change	0.92	0.71, 1.21	0.6		1.26	0.91, 1.75	0.2	
BOADICEA risk score	1.72	0.83, 3.58	0.1		4.48	1.56, 12.90	0.005	
BMI at baseline × BOADICEA score	0.93	0.79, 1.10	0.4		0.74	0.58, 0.95	0.02	
BMI change × BOADICEA score	1.08	0.92, 1.28	0.4		1.23	0.95, 1.59	0.1	

Abbreviations: ABCFR, Australian Breast Cancer Family Registry; ACCFR, Australasian Colorectal Cancer Family Registry; BMI, body mass index; BOADICEA, Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm (per 5%, adjusted for baseline age and age^2); CI, confidence interval; HR, hazard ratio; kConFab, Kathleen Cuningham Foundation Consortium for Research into Familial Breast Cancer; LL, log-likelihood.

[a] Adjusted for smoking and use of hormone replacement therapy.

[b] Change in LL from the base model that included smoking and use of hormone replacement therapy.

[c] Weight (kg)/height (m)^2.

[d] Change in BMI from ages 18–21 years to baseline.

[e] Adjusted for baseline age and age^2.

Even a null finding (not finding evidence of gene-environment interactions) is important because it could be used to support current practice, which typically assumes that the risk factors observed for the general population apply to people at high genetic risk. An increase in the absolute gradient in relative risk for people at higher genetic risk would have important implications because the gradient in absolute risk will be much greater for people at high genetic risk than it would be for the general population. A decrease in the absolute gradient in relative risk for people at higher genetic risk would also be important because this information could curtail inappropriate interventions and false advice for persons at the higher end of the risk spectrum.

Most studies of BMI and breast cancer risk use cohorts of women at average risk and have little statistical power to evaluate gene-environment interactions across the spectrum of risk. Using cohorts enriched for familial risk could help, as could better measures of family history risk and better measures of genetic risk. We used a prospective family cohort study design that provides increased information on familial and genetic risk through the study of multiple people in the same family (9). We have also used a cohort enriched for genetic risk of breast cancer through having oversampled women with a family history of breast cancer. This provides more statistical power by increasing the proportion of women at the upper end of the highly skewed genetic risk distribution. An early example of this approach in the context of a case-control study is the study by Becher et al. (26).

Our null findings should not be taken as showing that there are no multiplicative gene-environment interactions. There were 288 incident cases, so power was limited. We did not find any evidence that the BMI associations depended on age at baseline, when there is strong evidence that this is the case, at least for BMI at baseline. We did find, however, that there was evidence consistent with negative confounding between a protective association of BMI at ages 18–21 years and the opposite for BMI in later adulthood. Our measures of BMI at ages 18–21 years likely had greater imprecision than the measure of BMI at baseline, so there would have been less power to detect associations and interactions of the same magnitude for the latter BMI measure.

Our analyses can be used to predict statistical power for similarly structured cohorts. For example, the standard errors of the log hazard ratios for the BOADICEA interaction terms in Table 3 were 0.04 for models 9 and 10, so for these variables there was 80% power at the significance level of 0.05 (2-sided) to detect interactions of hazard ratio = 1.1 or more from this sample size. Given that standard errors are approximately inversely proportional to the square root of the number of incident cases, the detectable interaction

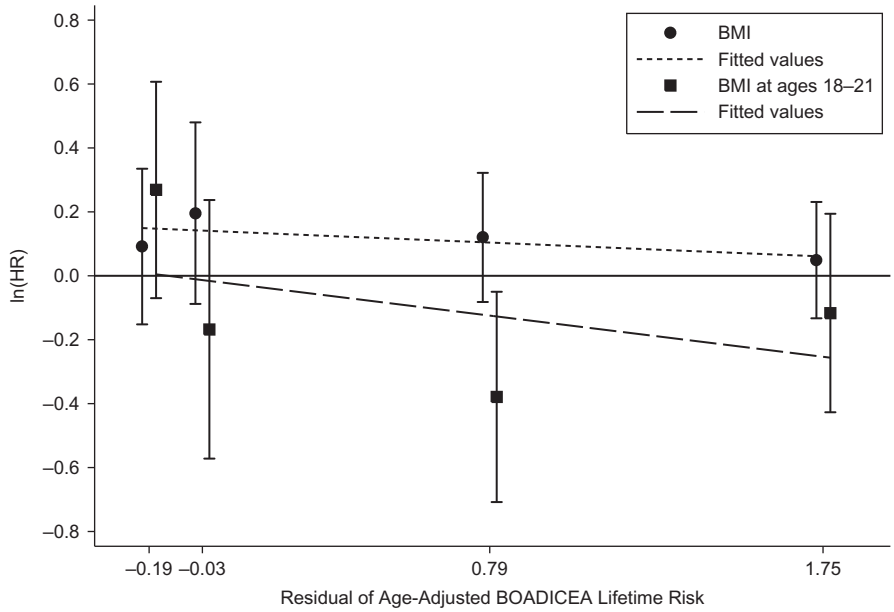

Figure 1. Logarithms of adjusted hazard ratios (HRs) for the risk of breast cancer according to body mass index (BMI; weight (kg)/height (m)^2) at baseline (per 5-unit increment) and BMI at ages 18–21 years (per 5-unit increment) in quartiles of the residuals of age-adjusted BOADICEA lifetime risk score (from left to right, median values from quartile 1 to quartile 4), Australia, 1992–2010. Bars, 95% confidence intervals. BOADICEA, Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm.

hazard ratio would be 1.06 for 1,000 incident cases and 1.03 for 4,000 incident cases.

We chose BMI because it is a potentially modifiable risk factor. Having a greater BMI has been shown to be associated with an increased risk of breast cancer for postmenopausal women (27–29), especially for women who are 15 years or more postmenopause (30) or aged 60 years or older (31). For premenopausal women, the risk associated with BMI is less

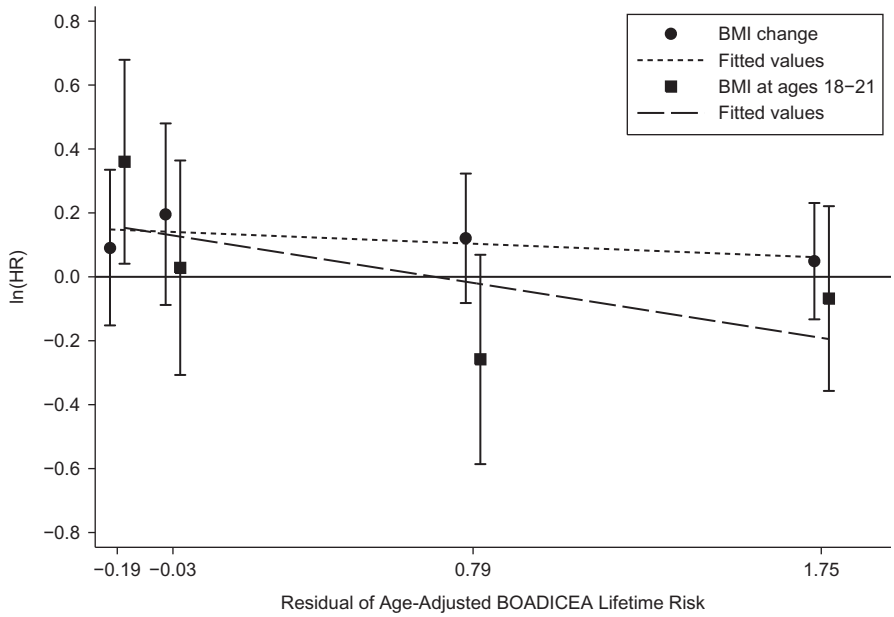

Figure 2. Logarithms of adjusted hazard ratios (HRs) for the risk of breast cancer according to change in body mass index (BMI; weight (kg)/height (m)^2) since baseline (per 5-unit increment) and BMI at ages 18–21 years (per 5-unit increment) in quartiles of the residuals of age-adjusted BOADICEA lifetime risk score (from left to right, median values from quartile 1 to quartile 4), Australia, 1992–2010. Bars, 95% confidence intervals. BOADICEA, Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm.

clear (27). In one recent meta-analysis of studies of risk for premenopausal women, Renehan et al. (29) concluded that having a greater BMI was associated with a decreased risk of breast cancer, while in another, Cheraghi et al. (28) found that the inverse risk association with BMI was not statistically significant. Greater BMI in childhood or adolescence has been found to be associated with decreased risk of both premenopausal and postmenopausal breast cancer (27), although a recent study found no evidence for an association between BMI at ages 18–21 years and postmenopausal breast cancer (32).

Given the emergence of better predictors of inherent risk through inclusion of genetic risk scores based on SNPs, the approach demonstrated here will be increasingly important, especially now that many of the major cohort studies across the world are including genetic risk measures. It is straightforward to include measured genetic risk factors in this prediction, as we have recently demonstrated (3). Genetic risk scores are likely to improve with the use of analytical approaches that focus on predicting risk (as distinct from discovering risk variants)—for example, by using different techniques for selecting SNPs, such as gene-based or pathway-based analyses of genome-wide association studies. Risk prediction will also improve by using more SNPs (33). This will all contribute to producing more power for detecting gene-environment interactions.

In summary, we have demonstrated the statistical power with which gene-environment interactions can be investigated using a cohort enriched for persons with increased genetic risk and a continuous measure of genetic risk based on family history. We plan to use the techniques described in this paper to study other potential multiplicative gene-environment interactions for breast cancer using a much larger prospective family study cohort enriched for familial risk by including families from the United States and Canada (9) and by using other cohorts from the Cancer Cohort Consortium (34). We think the approach demonstrated here is timely for the upcoming era of precision health.

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