TESTING FOR GENE–ENVIRONMENT INTERACTIONS USING A PROSPECTIVE FAMILY COHORT: BODY MASS INDEX IN EARLY AND LATER ADULTHOOD AND RISK OF BREAST CANCER

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Running head:

Testing for gene–environment interactions

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Abstract

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. But to do so we need to know if 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 three Australian cancer family cohorts, two 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 breast cancer associations with body mass index at age 18 to 21 years, body mass index at baseline, and change in body mass index, differed according to genetic risk based on lifetime breast cancer risk from birth estimated by the Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm 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 individuals with increased genetic risk and a continuous measure of genetic risk based on family history.

Keywords

breast cancer; BOADICEA; body mass index; cohort; familial risk; family study; gene–environment interaction

Abbreviations

ABCFR	Australian Breast Cancer Family Registry
ACCFR	Australian Colorectal Cancer Family Registry
BOADICEA	Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm
BMI	body mass index
CI	confidence interval
HR	hazard ratio
kConFab	Kathleen Cuningham Foundation Consortium for Research into Familial Breast Cancer
SD	standard deviation

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. But to do so, we need to know if 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 multi-generational family cancer history (3), can be used to develop risk predicting scores with an inter-quartile risk ratio of 5 or more (3). The cost of measuring genetic markers is decreasing and classification of risk is likely to improve by using genetic risk scores that are based on more markers, and perhaps using 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) estimates genetic risk by modeling major genes and polygenes (3-5). BOADICEA has been shown to be well calibrated and 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 epidemiological studies of breast cancer have measured both genetic and non-genetic risk factors comprehensively, and fewer have addressed gene–environment interactions by using global measures of genetic risk based on complex models of multi-generational 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 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 of breast cancer. 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 a prospective family cohort 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 the Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm (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 two correlated measurements: one in early adulthood and one in later life. Using this example, we consider the issue of multiple risk factors and allow 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.

MATERIALS AND METHODS

Subjects

We studied women who were unaffected with invasive breast cancer at enrolment into three large Australian cancer family 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).

ABCFR. From 1992 to 1999, probands and their relatives were recruited as described previously (11-16). Briefly, probands included population-based cases aged less than 60 years when diagnosed with 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 to 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) for which one or both 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 re-contacted at 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 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-degree and second-degree relatives and the date 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.

kConFab. Starting in 1997, families with multiple cases of breast cancer were recruited as described previously (17). Briefly, eligible families were identified from women attending 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 (*BRCA1*) or breast cancer 2, early onset (*BRCA2*) genes (18). At baseline, participants provided a blood sample for genetic analyses and completed the questionnaire used by the ABCFR (14).

Every three years, all female participants are invited to participate in the kConFab follow-up study, as described in detail previously (19). This study used a mailed self-administered questionnaire to systematically update the baseline questionnaire data, 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 Peter MacCallum Cancer Centre and from each of its recruitment sites. All participants provided written informed consent before taking part in the research.

ACCFR. From 1998 to 2007, families were recruited to 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-degree 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 them and their 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 cancer history information on all of their first-degree and second-degree relatives so that cancer history 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 five years and asked to complete a self-administered questionnaire to update data the information collected at baseline and to provide updated cancer histories for their first-degree 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 before baseline (unilateral or bilateral); they and their family had no deleterious mutations in *BRCA1*, *BRCA2*, or the tumor protein p53 (*TP53*) gene; they had completed a baseline questionnaire and provided data for all the height and weight questions. ABCFR participants were included if at least one member of their family had completed a follow-up questionnaire, while the kConFab participants were included if they had completed at least one 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 if at least one 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

The baseline risk factor questionnaires that were completed at enrolment into the cohorts, participants were asked about their height, their current weight and their weight

when aged between 18 and 21 years (or at age 20 years for the ACCFR). BMI at baseline and BMI aged 18 to 21 years were calculated as current weight (kg) and weight aged 18 to 21 years (kg), respectively, divided by the square of height (m) at baseline. Because there were so few missing values for the other risk factor questions used in analyses – 1 for smoking and 19 for HRT use – these were taken to be non-smokers or non-users, respectively.

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

For each eligible participant, we estimated genetic risk using BOADICEA to calculate the lifetime risk (from birth) of invasive breast cancer (4, 5) using baseline pedigree information from all participating and non-participating 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 was imputed using a previously developed protocol (14, 24). We adjusted BOADICEA lifetime risk for baseline age as a quadratic because we want 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 came first of last follow-up questionnaire, diagnosis of invasive breast cancer, death, mastectomy, oophorectomy, or age 80 years.

We fitted Cox proportional hazards models with age as the time axis and stratified by age at interview in two-year groups to estimate hazard ratios (HRs) for the risk of invasive breast cancer. Because our eligible participants included families with multiple members, robust estimates of confidence intervals (CI) were calculated by clustering by family. Tests of the proportional hazards assumption were based on Schoenfeld residuals.

We tested evidence for 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 was used for all statistical analyses (25). All statistical tests were two-sided and *P* values < 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 for more detail on the cohort.

Table 2 shows the distributions, unadjusted HRs and corresponding 95% CI 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 means (SD) were: 13.2% (SD = 5.5) for BOADICEA lifetime risk; 21.5 kg/m^2 (SD = 3.6) for BMI aged 18 to 21 years; 25.2 kg/m^2 (SD = 5.4) for BMI at baseline; 3.6 kg/m^2 (SD = 4.6) for change in BMI since age 18 to 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 and with having a first-degree relative with breast cancer (Table 2). The HRs for the continuous measurements were: 1.24 (95% CI: 1.14, 1.35; $P < 0.001$) for each 5% of BOADICEA lifetime risk; 1.07 (95% CI: 0.97, 1.19; $P = 0.2$) for each 5 kg/m^2 of BMI at baseline; 0.94 (95% CI: 0.79, 1.12; $P = 0.5$) for each 5 kg/m^2 of BMI aged 18 to 21 years; 1.13 (95% CI: 1.02, 1.26; $P = 0.02$) for each 5 kg/m^2 change in BMI since age 18 to 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 3 shows the fits for combinations of the BMI measures, age-adjusted BOADICEA, and their multiplicative interactions. Models I–III show that the only BMI measure associated with risk on its own was the change from BMI at 18–21 years to baseline ($P = 0.03$). Model IV shows that age-adjusted BOADICEA was strongly associated with

breast cancer risk ($P < 0.001$), and comparison with models V–VII show that this association did not change after adjusting for the BMI measures one at a time. Similarly, comparisons of models V–VII with models I–III, show that the BMI associations were unchanged after adjusting for age-adjusted BOADICEA.

Models VIII–X show that there was no evidence for a multiplicative interaction between any BMI measure and age-adjusted BOADICEA when considered alone (all $P > 0.1$).

Models XI–XIII considered the pairs of BMI measures, and all three gave similar fits with the same associations with age-adjusted BOADICEA. The associations with BMI at 18–21 years and BMI at baseline both diverge from the null when fitted together (models XI compared with models V and VI). After adjusting for BMI at 18–21 years, both BMI at baseline and BMI change were associated with an increased risk of breast cancer (both $P = 0.03$).

Models XIV–XVI considered the pairs of BMI measures, this time allowing for each measure to have a multiplicative interaction with age-adjusted BOADICEA (all models gave similar fits). After adjusting for BMI at 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 XI–XIII to models XIV–XVI was not significant ($P = 0.4$).

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

Figures 1 and 2 show the associations predicted by the two interaction models XIV and XV that include BMI at 18–21 years. Log HR estimates for both BMI measures tended to decrease with increasing age-adjusted BOADICEA. To illustrate interpretations, ignoring the lack of statistical evidence for multiplicative interactions, the predictions from these model

fits would be: (i) for women in the lower quartiles of age-adjusted BOADICEA, after taking into account BMI at age 18–21 years, both BMI at baseline and change in BMI, were associated with an increased risk of breast cancer, and (ii) for women in the upper quartile of age-adjusted BOADICEA, BMI at age 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. Non-multiplicative interactions or interactions involving individual SNPs could have been similarly considered by changing the model parameterization. We age-adjusted lifetime risk estimated by BOADICEA 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.

Even a null finding (not finding evidence of gene–environment interactions) is important because it could be used to support current practice that typically assumes that the risk factors 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 those 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 design that has increased information on familial and genetic risk by studying multiple people in the same family (9). We have also used a cohort enriched for genetic risk of breast cancer through having over-sampled women with a family history of breast cancer. This gives more 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 was by Becher et al. (26).

Our null findings should not be taken as showing 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 18–21 years and the opposite for BMI in later adulthood. Our measures of BMI at 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(HR) for the BOADICEA interaction terms in Table 3 were 0.04 for models IX and X, so for these variables there was 80% power at significance level 0.05 (two-sided) to detect interactions of HR = 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 HR 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 post-menopausal women (27-29), especially for women who are 15 years or more post-menopause (30) or aged 60 years or older (31). For pre-menopausal women, the risk associated with BMI is less clear (27). One recent meta-analysis of studies of risk for pre-menopausal women concluded that having a greater BMI was associated with a decreased risk of breast cancer (29), while another found that the inverse risk association with BMI was not statistically significant (28).

Greater BMI in childhood or adolescence has been found to be associated with decreased risk of both pre-menopausal and post-menopausal breast cancer (27), although a recent study has found no evidence for an association between BMI at age 18 to 21 years and post-menopausal breast cancer (32).

Given the emergence of better predictors of inherent risk by including 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 into this prediction, as we have recently demonstrated (3). Genetic risk scores are likely to improve with the use of analytic 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 giving more power for detecting gene–environment interactions. In summary, we have demonstrated the power with which gene–environment interactions can be investigated using a cohort enriched for individuals with increased genetic risk and a continuous measure of genetic risk based on family history. We plan to use the techniques 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 USA and Canada (9), and 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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FIGURE LEGENDS

Figure 1. Plots of the logarithm of the adjusted hazard ratios (HR) and corresponding 95% confidence intervals for the risk of breast cancer for body mass index (BMI) at baseline per 5 kg/m^2 and BMI aged 18–21 years per 5 kg/m^2 for quartiles of age-adjusted BOADICEA lifetime risk score, ABCFR, kConFab, and ACCFR, Australia, 1992–2010.

Figure 2. Plots of the logarithm of the adjusted hazard ratios (HR) and corresponding 95% confidence intervals for the risk of breast cancer for change in body mass index (BMI) since baseline per 5 kg/m^2 and BMI aged 18–21 years per 5 kg/m^2 for quartiles of age-adjusted BOADICEA lifetime risk score, ABCFR, kConFab, and ACCFR, Australia, 1992–2010.

TABLES

Table 1. Number of Families, Participants and Breast Cancers, and the Means and Standard Deviations for Number of Participants per Family, Age at Baseline, Years of Follow-Up, and Age at Diagnosis, by Source of Proband, ABCFR, kConFab, and ACCFR, Australia, 1992–2010.

Source of Proband	Families	Participants	Participants per Family		Age at Baseline (years)		Years of Follow-Up		Breast Cancers	Age at Diagnosis (years)	
	No.	No.	Mean	(SD)	Mean	(SD)	Mean	(SD)	No.	Mean	(SD)
ABCFR cases <40 years	418	1,168	2.8	(1.9)	50.7	(14.9)	14.1	(3.5)	64	62.7	(11.8)
ABCFR cases 40–49 years	254	571	2.2	(1.4)	47.3	(17.6)	13.6	(3.0)	31	58.0	(13.6)
ABCFR cases 50–59 years	225	556	2.5	(1.5)	43.2	(16.8)	14.0	(2.7)	20	57.9	(12.5)
ABCFR population controls <40 years	157	433	2.8	(1.6)	44.2	(14.5)	12.3	(1.9)	12	51.9	(12.2)
ABCFR population controls 40–49 years	154	359	2.3	(1.2)	45.6	(13.5)	11.7	(1.9)	9	58.6	(10.7)
ABCFR population controls 50–59 years	167	401	2.4	(1.5)	46.3	(14.8)	12.1	(2.0)	10	61.3	(10.1)
ABCFR twins	14	53	3.8	(2.4)	45.2	(15.1)	13.2	(2.2)	2	44.5	(4.9)
ABCFR Ashkenazi	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 <45 years	246	566	2.3	(1.5)	43.9	(14.8)	8.0	(2.9)	8	52.4	(12.5)
ACCFR cases 45–59 years	437	1,141	2.6	(1.7)	45.7	(14.5)	8.9	(2.5)	25	56.3	(11.1)
ACCFR 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. Frequency Distributions and Unadjusted Hazard Ratios, 95% Confidence Intervals, and *P* Values for the BOADICEA Risk Scores, Body Mass Index Measures, and Risk Factor Questions, ABCFR, kConFab, and ACCFR, Australia, 1992–2010.

Risk Factor	No.	%	HR	95% CI	*P* value
BOADICEA lifetime risk[a], %					
Q1: 0.29 to 9.51	2,228	24.4	Referent		
Q2: 9.52 to 11.03	2,301	25.2	1.01	0.65, 1.58	1.0
Q3: 11.04 to 16.27	2,287	25.1	1.81	1.27, 2.58	0.001
Q4: 16.28 to 59.09	2,310	25.3	2.16	1.52, 3.06	<0.001
Body mass index[b] aged 18–21 years[c]					
Q1: 11.34 to 19.15	2,181	23.9	Referent		
Q2: 19.16 to 20.93	2,382	26.1	1.03	0.75, 1.42	0.8
Q3: 20.94 to 23.06	2,280	25.0	0.89	0.64, 1.25	0.5
Q4: 23.07 to 68.69	2,283	25.0	0.92	0.66, 1.30	0.7
Body mass index[d], kg/m^2					
Q1: 11.72 to 21.45	2,230	24.4	Referent		
Q2: 21.46 to 24.02	2,324	25.5	1.18	0.84, 1.66	0.3
Q3: 24.03 to 27.68	2,276	24.9	1.34	0.94, 1.91	0.1
Q4: 27.69 to 65.75	2,296	25.2	1.26	0.88, 1.81	0.2
Change in body mass index[e]					
Q1: −45.18 to 0.39	2,281	25.0	Referent		
Q2: 0.40 to 2.71	2,380	25.0	1.16	0.78, 1.72	0.5
Q3: 2.72 to 5.86	2,270	24.9	1.56	1.09, 2.24	0.02
Q4: 5.87 to 40.40	2,295	25.1	1.52	1.05, 2.19	0.03
Country of birth					
Australia	7,430	81.4	Referent		
Overseas	1,693	18.6	0.79	0.59, 1.07	0.1
Missing	3	0.0			
Education, highest completed					
Year 10	1,908	20.9	Referent		
Year 11–12 or vocational	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	21	0.2			
Marital status					
Never married	1,365	15.0	Referent		
Married or living as married	7,748	84.9	1.28	0.75, 2.17	0.4
Missing	13	0.1			
Age at menarche, years					
<12	1,389	15.2	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	52	0.6			
Pregnant, ever					
No	1,865	20.4	Referent		
Yes	7,261	79.6	1.11	0.75, 1.63	0.6
Live birth, ever					
No	2,267	24.8	Referent		
Yes	6,859	75.2	1.10	0.76, 1.58	0.6

Risk Factor	No.	%	HR	95% CI	*P* value
Number of live births					
0	2,267	24.8	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	1	0.0			
Oral contraceptive use, ever					
No	1,931	21.2	Referent		
Yes	7,192	78.8			
Missing	3	0.0	1.06	0.77, 1.45	0.7
Menopause					
No	5,465	59.9	Referent		
Yes	3,661	40.1	0.71	0.41, 1.24	0.2
Hormone replacement therapy use, ever					
No	7,333	80.4	Referent		
Yes	1,774	19.4	1.33	0.99, 1.77	0.05
Missing	19	0.2			
Breast cancer in a first-degree relative					
No	5,267	57.7	Referent		
Yes	3,859	42.3	1.95	1.52, 2.50	<0.001
Smoking					
Never	4,968	54.4	Referent		
Past	2,557	28.0	1.08	0.83, 1.39	0.6
Current	1,600	17.5	0.68	0.46, 1.00	0.05
Missing	1	0.0			
Drink alcohol, ever					
No	3,626	39.7	Referent		
Yes	5,496	60.2	0.95	0.75, 1.20	0.7
Missing	4	0.0			

Abbreviations: ABCFR, Australian Breast Cancer Family Registry; ACCFR, Australasian Colorectal Cancer Family Registry; 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 medians: Q1, 9.09%; Q2, 9.86%; Q3, 13.74%; and Q4, 18.74%.

[b] kg/m^2

[c] Body mass index aged 18–21 years was divided into quartiles with the following medians: Q1, 18.25; Q2, 20.20; Q3, 21.91; and Q4, 24.91.

[d] Body mass index was divided into quartiles with the following medians: Q1, 19.95; Q2, 22.66; Q3, 25.56; and Q4, 31.17.

[e] Change in body mass index was divided into quartiles with the following medians: Q1, 0.00; Q2, 1.63; Q3, 4.06; and Q4, 8.65.

Table 3. Adjusted Hazard Ratios, 95% Confidence Intervals, and *P* Values for the Risk of Breast Cancer for Body Mass Index and BOADICEA Risk Score, ABCFR, kConFab, and ACCFR, Australia, 1992–2010.

Model and Adjustment Criteria	HR[a]	95% CI	*P*	Δ LL[b]
I				0.17
BMI at 18–21 years (per 5 kg/m^2)	0.95	0.80, 1.13	0.5	
II				0.77
BMI at baseline (per 5 kg/m^2)	1.07	0.97, 1.19	0.2	
III				1.70
BMI change (per 5 kg/m^2)	1.13	1.01, 1.25	0.03	
IV				9.61
BOADICEA (per 5%; adjusted for baseline age and age^2)	1.24	1.14, 1.35	<0.001	
V				9.76
BMI at 18–21 years (per 5 kg/m^2)	0.95	0.80, 1.13	0.6	
BOADICEA (per 5%; adjusted for baseline age and age^2)	1.24	1.14, 1.35	<0.001	
VI				10.57
BMI at baseline (per 5 kg/m^2)	1.08	0.98, 1.20	0.1	
BOADICEA (per 5%; adjusted for baseline age and age^2)	1.25	1.15, 1.36	<0.001	
VII				11.59
BMI change (per 5 kg/m^2)	1.14	1.02, 1.27	0.02	
BOADICEA (per 5%; adjusted for baseline age and age^2)	1.25	1.15, 1.36	<0.001	
VIII				10.40
BMI at 18–21 years (per 5 kg/m^2)	1.02	0.85, 1.24	0.8	
BOADICEA (per 5%; adjusted for baseline age and age^2)	1.79	0.94, 3.43	0.08	
BMI at 18–21 years (per 5 kg/m^2) × BOADICEA (per 5%; adjusted for baseline age and age^2)	0.92	0.78, 1.07	0.3	

Model and Adjustment Criteria	HR[a]	95% CI	*P*	Δ LL[b]
IX				11.50
BMI at baseline (per 5 kg/m^2)	1.14	1.01, 1.28	0.03	
BOADICEA (per 5%; adjusted for baseline age and age^2)	1.70	1.12, 2.57	0.01	
BMI at baseline (per 5 kg/m^2) × BOADICEA (per 5%; adjusted for baseline age and age^2)	0.94	0.87, 1.02	0.1	
X				11.83
BMI change (per 5 kg/m^2)	1.17	1.03, 1.33	0.02	
BOADICEA (per 5%; adjusted for baseline age and age^2)	1.28	1.16, 1.42	<0.001	
BMI change (per 5 kg/m^2) × BOADICEA (per 5%; adjusted for baseline age and age^2)	0.97	0.90, 1.04	0.4	
XI				11.64
BMI at 18–21 years (per 5 kg/m^2)	0.86	0.71, 1.03	0.1	
BMI at baseline (per 5 kg/m^2)	1.14	1.02, 1.27	0.03	
BOADICEA (per 5%; adjusted for baseline age and age^2)	1.25	1.15, 1.36	<0.001	
XII				11.64
BMI at 18–21 years (per 5 kg/m^2)	0.97	0.82, 1.16	0.8	
BMI change (per 5 kg/m^2)	1.14	1.02, 1.27	0.03	
BOADICEA (per 5%; adjusted for baseline age and age^2)	1.25	1.15, 1.36	<0.001	
XIII				11.64
BMI at baseline (per 5 kg/m^2)	0.97	0.82, 1.16	0.8	
BMI change (per 5 kg/m^2)	1.17	0.97, 1.40	0.1	
BOADICEA (per 5%; adjusted for baseline age and age^2)	1.25	1.15, 1.36	<0.001	

Model and Adjustment Criteria	HR[a]	95% CI	*P*	Δ LL[b]
XIV				12.69
BMI at 18–21 years (per 5 kg/m^2)	0.90	0.73, 1.12	0.3	
BMI at baseline (per 5 kg/m^2)	1.18	1.04, 1.34	0.01	
BOADICEA (per 5%; adjusted for baseline age and age^2)	1.97	0.98, 3.96	0.06	
BMI at 18–21 years (per 5 kg/m^2) × BOADICEA (per 5%; adjusted for baseline age and age^2)	0.95	0.81, 1.11	0.5	
BMI at baseline (per 5 kg/m^2) × BOADICEA (per 5%; adjusted for age and age^2)	0.95	0.88, 1.04	0.3	
XV				12.69
BMI at 18–21 years (per 5 kg/m^2)	1.06	0.87, 1.30	0.6	
BMI change (per 5 kg/m^2)	1.18	1.04, 1.34	0.01	
BOADICEA (per 5%; adjusted for baseline age and age^2)	1.97	0.98, 3.96	0.06	
BMI at 18–21 years (per 5 kg/m^2) × BOADICEA (per 5%; adjusted for baseline age and age^2)	0.90	0.77, 1.06	0.2	
BMI change (per 5 kg/m^2) × BOADICEA (per 5%; adjusted for baseline age and age^2)	0.95	0.88, 1.04	0.3	
XVI				12.69
BMI at baseline (per 5 kg/m^2)	1.06	0.87, 1.30	0.6	
BMI change (per 5 kg/m^2)	1.11	0.90, 1.38	0.3	
BOADICEA (per 5%; adjusted for baseline age and age^2)	1.97	0.98, 3.96	0.06	
BMI at baseline (per 5 kg/m^2) × BOADICEA (per 5%; adjusted for baseline age and age^2)	0.90	0.77, 1.06	0.2	
BMI change (per 5 kg/m^2) × BOADICEA (per 5%; adjusted for baseline age and age^2)	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 (kg/m^2); BMI change, difference in body mass index (kg/m^2) from age 18–21 years to baseline; 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 hormone replacement therapy use.

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

Table 4. Adjusted Hazard Ratios, 95% Confidence Intervals, and *P* Values for the Risk of Breast Cancer for Body Mass Index and BOADICEA Risk Score by Menopausal Status, ABCFR, kConFab, and ACCFR, Australia, 1992–2010.

	Premenopausal				Postmenopausal			
Model and Adjustment Criteria	**HR[a]**	**95% CI**	***P***	**Δ LL[b]**	**HR[a]**	**95% CI**	***P***	**Δ LL[b]**
I				0.34				1.78
BMI 18–21	1.01	0.89, 1.36	0.4		0.76	0.58, 0.99	0.04	
II				0.79				0.04
BMI baseline	1.10	0.96, 1.26	0.2		1.03	0.88, 1.21	0.7	
III				0.43				1.20
BMI change	1.10	0.93, 1.29	0.3		1.14	0.99, 1.33	0.08	
IV				7.61				2.30
BOADICEA	1.27	0.16, 1.40	<0.001		1.20	1.03, 1.41	0.02	
V				7.99				4.14
BMI 18–21	1.11	0.90, 1.37	0.3		0.76	0.58, 0.98	0.04	
BOADICEA	1.26	1.16, 1.40	<0.001		1.20	1.03, 1.40	0.02	
VI				8.64				2.38
BMI baseline	1.11	0.97, 1.27	0.1		1.04	0.88, 1.22	0.7	
BOADICEA	1.28	1.16, 1.41	<0.001		1.20	1.03, 1.41	0.02	
VII				8.24				3.64
BMI change	1.12	0.95, 1.31	0.2		1.15	0.99, 1.34	0.07	
BOADICEA	1.28	1.16, 1.41	<0.001		1.21	1.03, 1.41	0.02	

	Premenopausal				Postmenopausal			
Model and Adjustment Criteria	**HR[a]**	**95% CI**	***P***	**Δ LL[b]**	**HR[a]**	**95% CI**	***P***	**Δ LL[b]**
VIII				8.37				5.66
BMI 18–21	1.12	0.94, 1.53	0.1		0.89	0.67, 1.18	0.4	
BOADICEA	1.74	0.87, 3.47	0.1		3.66	1.40, 9.58	0.008	
BMI 18–21 × BOADICEA	0.93	0.79, 1.09	0.4		0.76	0.60, 0.97	0.03	
IX				8.72				3.60
BMI baseline	1.14	0.97, 1.35	0.1		1.12	0.94, 1.32	0.2	
BOADICEA	1.44	0.88, 2.34	0.1		2.43	1.12, 5.27	0.03	
BMI × BOADICEA	0.98	0.88, 1.08	0.6		0.87	0.75, 1.01	0.08	
X				8.26				3.79
BMI change	1.10	0.91, 1.33	0.3		1.19	0.99, 1.43	0.07	
BOADICEA	1.27	1.14, 1.41	<0.001		1.27	1.00, 1.62	0.05	
BMI change × BOADICEA	1.02	0.91, 1.13	0.8		0.95	0.83, 1.10	0.5	
XI				8.64				4.91
BMI 18–21	0.99	0.77, 1.28	1.0		0.70	0.53, 0.92	0.01	
BMI baseline	1.12	0.96, 1.30	0.2		1.12	0.95, 1.32	0.2	
BOADICEA	1.28	1.16, 1.41	<0.001		1.21	1.03, 1.41	0.02	
XII				8.64				4.91
BMI 18–21	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	1.28	1.16,1.41	<0.001		1.21	1.03, 1.41	0.02	

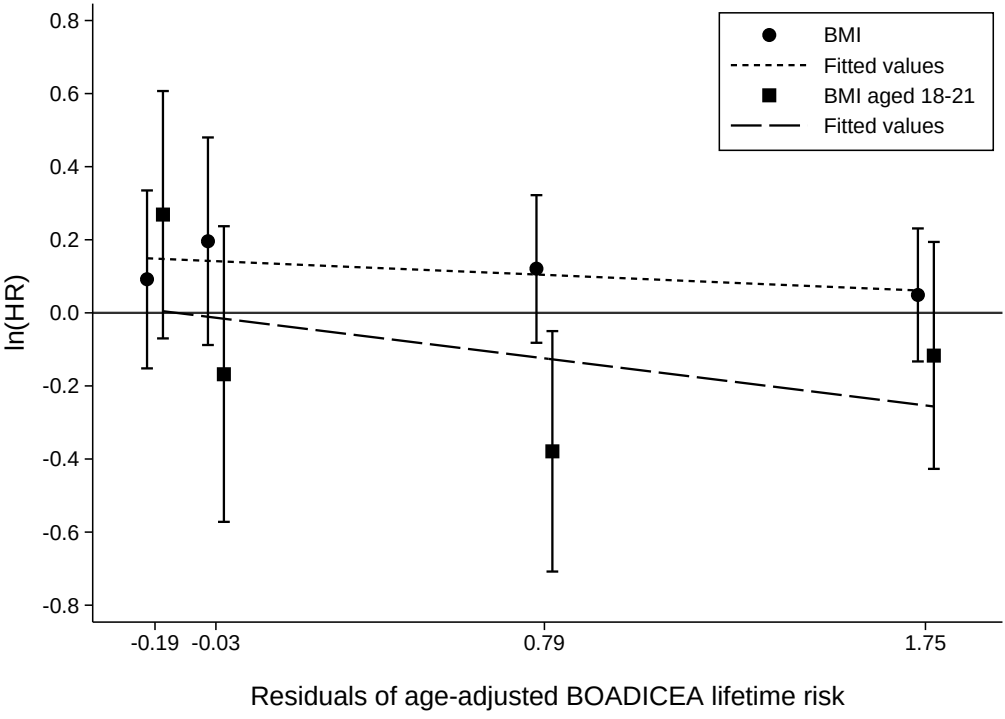
	Premenopausal				Postmenopausal			
Model and Adjustment Criteria	**HR[a]**	**95% CI**	***P***	**Δ LL[b]**	**HR[a]**	**95% CI**	***P***	**Δ LL[b]**
XIII				8.64				4.91
BMI baseline	1.11	0.90, 1.37	0.3		0.79	0.60, 1.04	0.09	
BMI change	1.01	0.78, 1.29	1.0		1.42	1.08, 1.87	0.01	
BOADICEA	1.28	1.16, 1.41	<0.001		1.21	1.03, 1.41	0.02	
XIV				12.01				6.87
BMI 18–21	1.08	0.83, 1.42	0.6		0.79	0.57, 1.10	0.2	
BMI baseline	1.11	0.92, 1.33	0.3		1.17	0.97, 1.42	0.09	
BOADICEA	1.72	0.83, 3.58	0.1		4.48	1.56, 12.90	0.005	
BMI 18–21 × BOADICEA	0.92	0.87, 1.09	0.4		0.81	0.63, 1.05	0.1	
BMI baseline × BOADICEA	1.01	0.91, 1.12	0.9		0.91	0.78, 1.07	0.2	
XV				12.01				6.87
BMI 18–21	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	1.72	0.83, 3.58	0.1		4.48	1.56, 12.90	0.005	
BMI 18–21 × BOADICEA	0.93	0.79, 1.01	0.4		0.74	0.58, 0.95	0.02	
BMI change × BOADICEA	1.01	0.91, 1.23	0.9		0.91	0.78, 0.95	0.2	
XVI				12.01				6.87
BMI 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	1.72	0.83, 3.58	0.1		4.48	1.56, 12.90	0.005	
BMI baseline × BOADICEA	0.93	0.79, 1.10	0.4		0.74	0.58, 0.95	0.02	
BMI change × BOADICEA	1.08	0.92, 1.28	0.4		1.23	0.95, 1.59	0.1	

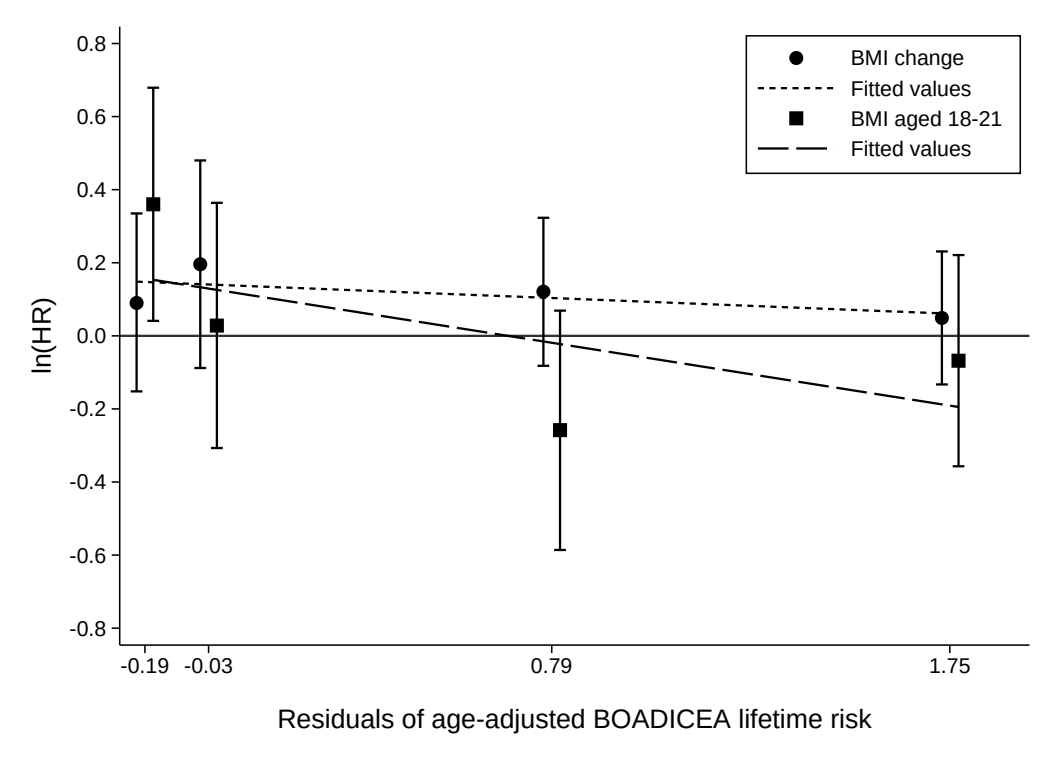
Abbreviations: ABCFR, Australian Breast Cancer Family Registry; ACCFR, Australasian Colorectal Cancer Family Registry; BMI 18–21, body mass index at age 18 to 21 years (per 5 kg/m^2); BMI baseline, body mass index at baseline (per 5 kg/m^2); BMI change, difference in body mass index from age 18–21 years to baseline (per 5 kg/m^2);

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 hormone replacement therapy use.

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


BMI
Fitted values
BMI aged 18-21
Fitted values
ln(HR)
0.8
0.6
0.4
0.2
0.0
-0.2
-0.4
-0.6
-0.8
-0.19
-0.03
0.79
1.75
Residuals of age-adjusted BOADICEA lifetime risk


BMI change
Fitted values
BMI aged 18-21
Fitted values
ln(HR)
0.8
0.6
0.4
0.2
0.0
-0.2
-0.4
-0.6
-0.8
-0.19
-0.03
0.79
1.75
Residuals of age-adjusted BOADICEA lifetime risk