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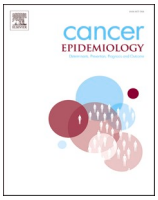

BMI and breast cancer risk around age at menopause

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ABSTRACT

Background: A high body mass index (BMI, kg/m^2) is associated with decreased risk of breast cancer before menopause, but increased risk after menopause. Exactly when this reversal occurs in relation to menopause is unclear. Locating that change point could provide insight into the role of adiposity in breast cancer etiology.
Methods: We examined the association between BMI and breast cancer risk in the Premenopausal Breast Cancer Collaborative Group, from age 45 up to breast cancer diagnosis, loss to follow-up, death, or age 55, whichever came first. Analyses included 609,880 women in 16 prospective studies, including 9956 who developed breast cancer before age 55. We fitted three BMI hazard ratio (HR) models over age-time: constant, linear, or nonlinear (via splines), applying piecewise exponential additive mixed models, with age as the primary time scale. We divided person-time into four strata: premenopause; postmenopause due to natural menopause; postmenopause because of interventional loss of ovarian function (bilateral oophorectomy (BO) or chemotherapy); postmenopause due to hysterectomy without BO. Sensitivity analyses included stratifying by BMI in young adulthood, or excluding women using menopausal hormone therapy.
Results: The constant BMI HR model provided the best fit for all four menopausal status groups. Under this model, the estimated association between a five-unit increment in BMI and breast cancer risk was HR=0.87 (95% CI: 0.85, 0.89) before menopause, HR=1.00 (95% CI: 0.96, 1.04) after natural menopause, HR=0.99 (95% CI: 0.93, 1.05) after interventional loss of ovarian function, and HR=0.88 (95% CI: 0.76, 1.02) after hysterectomy without BO.
Conclusion: The BMI breast cancer HRs remained less than or near one during the 45–55 year age range indicating that the transition to a positive association between BMI and risk occurs after age 55.

1. Introduction

Direction of associations between body mass index (BMI, kg/m^2) and breast cancer risk depends on menopausal status [1]. A wide body of evidence supports an inverse association between BMI and breast cancer risk before menopause [2–7]. Higher young adult BMI is a protective factor for breast cancer incidence [6,8] and may have the potential to modify patterns in estimated BMI HRs later in life. Following menopause, this inverse association changes to a positive association [5, 9–12]. With this evidence prior to and after menopause, along this continuum on an age scale, it is clear that the association between BMI and breast cancer risk changes from a protective to a deleterious association. Although potential biological mechanisms have been proposed to explain the difference in associations between BMI and breast cancer by menopausal status [1], the time-course for this reversal has not been well described, particularly in relation to type of menopause.

Including menopausal status as an effect measure modifier of the association between BMI and breast cancer risk is one analytic approach to model associations between BMI and breast cancer risk dependent on menopause. Evaluation of these associations can entail inclusion of a product term between a continuous constant BMI variable and a binary menopause variable in a regression model [13]. These types of analyses assume a constant hazard ratio (HR) over time allowing for an abrupt shift at menopause, but age-time dependent changes in these associations remain unknown and may be more gradual or vary by type of menopause. Describing changes in associations between BMI and breast cancer risk around the typical age at menopausal transition may provide a better understanding of these temporal patterns.

Given the lack of evidence assessing changes in the associations between BMI and breast cancer risk around ages of menopausal transition, our primary aim was to describe patterns of change over age-time in the association between BMI and breast cancer risk from 45 to 55 years. We examined the change in the associations between BMI and breast cancer risk across the age-time scale by menopausal status using a large consortium-based pooled sample from 16 cohorts.

2. Methods

2.1. Study sample

The Premenopausal Breast Cancer Collaborative Group (PBCCG) includes over 1 million participants from 23 cohorts meeting eligibility requirements of at least 100 female breast cancer diagnoses during follow-up before age 55 years and data collection occurring at least at two time points [14]. To accommodate our primary aim of estimating breast cancer incidence in relation to an age-time-dependent menopause status variable, we included the 16 cohorts with participants reporting both age at menopause and a cause of menopause after the following exclusions. We excluded women: (i) without at least one BMI measurement (n=13,367); (ii) postmenopausal women with missing age at or cause of menopause (n=111,117); (iii) postmenopausal women with no BMI ascertained after menopause (n=512); (iv) no BMI ascertained between the ages of 40–55 years (n=138,005); (v) women from cohorts with fewer than 20 breast cancer diagnoses (n=155,813); (vi) women with no person-time between ages 45 and 55 years (n=17,279); and (vii) women with implausible BMI values (n=40). With these exclusions, 609,880 participants remained in the analysis (Supplemental Figure 1).

Approval from institutional review boards and individual consent for all cohorts in the PBCCG conformed to each study's ethics review requirements.

2.2. Body mass index

We included BMI (in kg/m^2) in the models as a continuous variable, with results reported per 5-unit increment. BMI values ascertained included BMI reported at study entry, which we updated for each age-time interval with any follow-up BMI to create a time-dependent covariate. If there was no BMI reported for a particular person-year, we used BMI from the preceding person-year for the individual. For example, if a person did not report any new BMI during the follow up period, their BMI at entry to their age-time period was used for each

[1] Equal contribution as senior authors.

subsequent age-time interval.

The interval between ages 45 and 55 was of most interest because the median age at menopause is around age 51 years [15–17]. We included person-time based on BMI most proximal to this time range dependent on menopausal status. For premenopausal person-time, we included BMI reported at most five years prior to this interval. For analyses including postmenopausal person-time, we used BMI reported within three years prior to the age at menopause. For the 609,880 women in the study sample, there was a median (interquartile range) of 2 (1,3) BMI observations.

2.3. Statistical methods

We used frequencies and percentages to describe categorical variables, and medians and interquartile ranges to describe the continuous variables for sample characteristics.

To estimate breast cancer HRs for BMI as continuous time-dependent variables by menopausal status, we used piecewise exponential additive mixed modeling (PAMM) [18] with age as the time scale. This method provides estimates similar to Cox proportional hazards models, and it is more versatile in specifying smooth age-time-varying coefficient estimates with cohort strata. In brief, the simpler piecewise exponential model (PEM) enabled us to divide person-time into year intervals on the age scale and estimate a constant hazard within each interval using a Poisson-likelihood method. The PAMM model extends the PEM with an additive component to allow for more complex smooth time-varying effects of covariates and the underlying baseline hazard. The PAMM approach allows estimation of 95% confidence intervals (CIs) for models including splines of time-varying covariates and coefficients in time-to-event analyses along with cohort strata, as we specified in our models.

Age was the primary time scale to estimate three time-related BMI breast HRs: constant, linear change over age-time, or nonlinear (via splines) change. We specified the best fitting model after evaluating the Akaike's Information Criterion (AIC) and residual deviance with chi-square tests comparing the three models mentioned above.

We evaluated heterogeneity of our estimates across cohorts before pooling the data [14]. To do this, we estimated cohort-specific estimates and estimated the I^2 term from a meta-analysis to evaluate heterogeneity of estimates across studies [19].

Sensitivity analyses included three different types of analyses. A first set of sensitivity analyses included estimation of BMI-breast cancer HRs after stratifying by overweight status (BMI$\geq$25 kg/m^2) at age 18–24 years. A second set of sensitivity analyses included assessing associations in a subgroup of women who reported never using menopausal hormone therapy (MHT) at baseline, because such use could cause inaccuracies in the reported age at menopause and consequently influence the estimated patterns of BMI HR over age-time. Also, the relationship between BMI and postmenopausal breast cancer may depend on MHT [20]. Sample size for this group only allowed estimates for the natural and premenopausal groups of women. Both overweight status at age 18–24 and MHT variables were not available across all 16 cohorts, and subsets were analyzed for each of these sensitivity analyses. Last, we changed the time scale for the postmenopausal person time to time since menopause instead of an age scale and adjusted for age (in years) at baseline.

2.4. Menopausal status

All analyses were stratified into menopausal groups: 1) premenopausal, 2) natural menopause, 3) medically induced loss of ovarian function and 4) hysterectomy without bilateral oophorectomy (BO). The "loss of ovarian function" group (group 3) mainly included women reporting BO as well as chemotherapy. For the fourth group, the timing of hormonal menopause is not known, and we instead used person-time starting at the hysterectomy without BO. In the analyses, we divided person-time, as defined above, according to the four menopausal groups and fitted those person-times in separate models between 45 and 55 years of age. For example, a woman who experienced natural menopause after study entry had person-time that was partitioned into two separate models: 1) the premenopausal person-time, from her study entry until one year following the reported age at last menstrual period, and 2) the natural menopause person-time, which includes time from one year after cessation of menstruation until either an event or censoring, whichever occurred first. Menopausal status was lagged by one year for all participants to account for menopause occurrence due to breast cancer treatments in year of diagnosis [6].

We used R software [21], version 4.0.2, to manage the harmonized data from the PBCCG and conduct all statistical analyses.

3. Results

We used person-time in years from 609,880 women including incident breast cancer between ages 45–55 years and followed for a median (IQR) of 5.0 (4.0, 10.0) years from a total of 16 cohorts in the PBCCG (Table 1, Supplemental Table 1). The median age at entry (IQR) was 42.6 (37.0, 47.7) years. Most women self-identified as white or of European ancestry (n=391,561, 82.5%). Within the 45–55 year age interval, a total of 9956 developed incident breast cancer, 387,623 women were postmenopausal at entry, and 183,744 reported menopause during follow-up.

In assessing change in the association between BMI and breast cancer risk over age-time across the cohorts we did not find strong heterogeneity across samples for any of the menopausal groups, which supported the validity of pooling data from all the cohorts (Supplemental Figure 2). Similarly, the between-cohort heterogeneity in constant BMI HR estimates was low enough to allow pooling of the data across cohorts (Supplemental Figure 3).

After evaluating the three models to assess the BMI HR change over age-time between 45 and 55 years of age for the four menopause groups, we found no evidence to support either a linear or non-linear change in the BMI HR over age-time compared with a constant BMI HR model for

Table 1
Descriptive statistics for analytic sample.

	Overall
Number of women	609,880
Age at menopause (at baseline)	47.0 [42.0, 50.0]
Participant age at entry	42.6 [37.0, 47.7]
Age at menarche	13.0 [12.0, 13.0]
Follow-up time (years) between age 45–55 years	5.0 [4.0, 10.0]
BMI	23.3 [21.2, 26.6]
BMI, 18–24 years	20.8 [19.3, 22.7]
BMI>=25 kg/m^2, 18–24 years	46,579 (10.8)
Cause of menopause, baseline	
Hysterectomy without bilateral oophorectomy	35,525 (9.2)
Medically induced loss of ovarian function	70,432 (18.2)
Natural	281,666 (72.7)
Age at first birth	
Nulliparous	121,033 (19.8)
$\leq$ 20	65,983 (10.8)
21–24	172,932 (28.4)
25–29	174,825 (28.7)
30–55	75,107 (12.3)
Ethnicity	
African ancestry	58,132 (12.2)
Asian	17,430 (3.7)
European ancestry	391,561 (82.5)
Other	7714 (1.6)
Menopausal hormone therapy (at baseline)	53,174 (21.7)
Breast Cancers	9,956 (1.6)

Note:
All age variables are in year units, continuous variables are characterized by median.
[interquartile range], and categorical variables are characterized by number of observations (percent).

any of the menopause categories (Table 2, Supplemental Table 2, and Supplemental Figure 4). The estimated ratio of BMI-breast cancer HRs for a one-year change in age-time was close to one for all four menopausal groups suggesting little change in BMI breast cancer HRs over this age interval. Similarly, the estimated BMI breast cancer HRs at ages 45, 50, and 54 years in the nonlinear over age-time spline model indicated BMI breast cancer HRs close to the HR estimated from the constant HR model (Table 2). The constant BMI (per 5 kg/m^2 increment) HR (95% CI) was 0.87 (0.85, 0.89) for the premenopausal group, 0.88 (0.76, 1.02) for the hysterectomy without bilateral oophorectomy group, 1.00 (0.96, 1.04) for the natural menopause group, 0.99 (0.93, 1.05) for the loss of ovarian function group (Table 2). Comparing models with and without the constant BMI term, we found no evidence for a BMI HR that differed from 1 for the postmenopausal groups, suggesting a null association between BMI and breast cancer risk for postmenopausal women under age 55 years.

We conducted sensitivity analyses to determine any changes in the interpretation of our findings. The first and second set of analyses either stratified by young adult overweight status or restricting the sample to women who did not report ever taking menopausal hormone therapy at study entry. Both the first and second set of sensitivity analyses included a subset of cohorts from the primary sample that had information on either early life BMI or menopausal hormone therapy, and the HRs for the subsets were slightly different from those from the primary analyses. Last, we evaluated models with time since menopause as the time scale.

In analyses stratifying by young adult overweight status (BMI>=25 kg/m^2) at 18–24 years of age (Table 3), the best fitting model remained the constant BMI breast cancer HR. For women reporting overweight at ages 18–24 years, the BMI breast cancer HR (95% CI) estimate was 0.75 (0.45, 1.22) for the hysterectomy without BO group, 1.07 (0.93, 1.23) for the natural menopause group, and 1.10 (0.93, 1.31) for the loss of ovarian function menopause group. Among women not reporting overweight at ages 18–24 years, the estimates were similar. Except for the natural menopause group who were not overweight, we found no evidence of the constant BMI breast cancer HRs differing from the ones for the postmenopausal groups in either strata. The BMI HR for the premenopausal group of women not reporting overweight in young adulthood suggested a protective relationship that was similar to that for the group of women reporting overweight in young adulthood.

When we restricted analyses to women who, at the start of the 45–55 year interval, reported never using menopausal hormone therapy, the models with a constant BMI HR over age-time remained the best fitting (Table 4). For the natural menopause group, estimates for the never use group were similar to ones using the full sample. As in the primary analyses, the premenopausal group not reporting menopausal hormone therapy use had an inverse HR (0.89 (95% CI: 0.85, 0.93)). In the last set of sensitivity analyses, the best fitting model was the constant BMI breast cancer HR over time since menopause (Supplemental Table 3). These results did not substantively change from the primary analyses using age as the time scale.

4. Discussion

Considering each of the four menopausal groups separately, we found little evidence of changes in the BMI breast cancer HRs over age-time during the age range covering the most common period of transition to menopause, ages 45–55 years. BMI was inversely associated with breast cancer risk for premenopausal women. The BMI breast cancer HR was close to one for women who had experienced natural or loss of ovarian function and were between 45 and 55 years; we found little evidence of any change in this association between BMI and breast cancer risk with increasing age in our primary analysis. These findings did not differ by overweight in early adulthood or for women not on MHT at baseline.

Our results confirm previous findings in this consortium of inverse associations between BMI and premenopausal breast cancer [6]. A meta-analysis of risk estimates from 34 data sources yielded a BMI relative risk (95% CI) of 0.92 (per 5-unit increment in BMI (kg/m^2)) (0.88, 0.97) for premenopausal breast cancer [5]. Analysis of four studies found a pooled relative risk (95% CI) of 0.89 (0.81, 0.97) [7]. These estimates were similar to those reported previously in the PBCCG [6].

Our findings for postmenopausal women are not consistent with those from previous publications, but most have included postmenopausal women across much broader age ranges. For example, a meta-analysis of 31 studies examining the association between postmenopausal breast cancer incidence and BMI indicated a relative risk (95% CI) of 1.12 (1.08, 1.16) [5] for a 5 unit increment. In the United States Women's Health Initiative [9], the overall invasive breast cancer HR was 1.17 (95% CI: 1.06, 1.29) for women with overweight compared to women who were not with overweight between 50 and 79 years with a median 13 years follow-up time. The BMI HR (95% CI) increased with age — the HR (95% CI) comparing overweight to non-overweight groups was 1.02 (0.87, 1.20) for women 50–59 years at baseline and 1.29 (1.03, 1.62) for women 70–79 years old at baseline. Another study showed a breast cancer relative risk (95% CI) of 1.29 (per 5 unit difference) (1.22, 1.36) for women with obesity compared to the non-obese BMI group in postmenopausal women who at baseline reported never using MHT [10]. The narrower and earlier age range covered by our analysis thus may explain the lower HR found in our analysis of postmenopausal women. Given our null postmenopausal BMI HR estimates compared with previous analyses, our data are most consistent with the

Table 2
Breast cancer hazard ratios[a] (HRs) per 5-unit change in BMI by model type.

			Model 1: Constant BMI		Model 2: Linear BMI			Model 3: HR estimates based on spline model		
Menopause status	n, cases	person-years	HR (95% CI)	p-value[b]	linear HR intercept term[c] (95% CI)	linear HR slope term[d] (95% CI)	pvalue[e]	HR at age 45	HR at age 50	HR at age 54
Premenopausal	6,886	2,541,743	0.87 (0.85,0.89)	0	0.86 (0.83,0.90)	1.00 (0.99,1.01)	0.079	0.86 (0.82,0.90)	0.87 (0.85,0.90)	0.88 (0.83,0.94)
Hysterectomy without bilateral oophorectomy	184	57,467	0.88 (0.76,1.02)	0.087	0.93 (0.64,1.35)	0.99 (0.94,1.05)	0.773	0.93 (0.63,1.36)	0.89 (0.76,1.05)	0.86 (0.69,1.07)
Natural	2,058	818,476	1.00 (0.96,1.04)	1	0.93 (0.79,1.10)	1.01 (0.99,1.03)	0.242	0.93 (0.79,1.10)	0.98 (0.92,1.04)	1.02 (0.96,1.08)
Loss of ovarian function	828	367,675	0.99 (0.93,1.05)	1	0.98 (0.84,1.13)	1.00 (0.98,1.03)	1	0.98 (0.84,1.14)	0.98 (0.92,1.05)	0.99 (0.90,1.09)

[a] All analyses are stratified by cohort.
[b] p-value for Chi-square test for difference from null model (no BMI term).
[c] HR at age 45 years
[d] Ratio of HR for a one-year change in age-time.
[e] p-value for Chi-square test for difference from constant BMI model.

Table 3
Breast cancer hazard ratios[a] (HRs) per 5-unit change in BMI by overweight (BMI>=25 kg/m2) strata at age 18–24 years.

	Overweight at ages 18–24 years							Not overweight at ages 18–24 years						
			Model 1: Constant BMI		Model 2: Linear BMI					Model 1: Constant BMI		Model 2: Linear BMI		
Menopause status	n, cases	person-years	HR (95% CI)	p-value[b]	linear HR intercept[c] (95% CI)	linear HR term[d] (95% CI)	p-value[e]	n, cases	person-	HR (95% CI)	p-value[b]	linear HR intercept[c] (95% CI)	linear HR term[d] (95% CI)	p-value[e]
Premenopausal	351	196,081	0.94 (0.87,1.02)	0.116	0.88 (0.77, 1.01)	1.02 (0.99, 1.05)	0.229	4,381	1,689,521	0.92 (0.88, 0.95)	<0.001	0.91 (0.86, 0.97)	1.00 (0.99, 1.02)	0.487
Hysterectomy without bilateral oophorectomy	14	6392	0.75 (0.45,1.22)	0.228	1.49 (0.36, 6.22)	0.90 (0.73, 1.11)	0.351	165	49,943	0.94 (0.79, 1.13)	0.503	0.97 (0.63, 1.51)	0.99 (0.93, 1.06)	0.872
Natural	93	57,008	1.07 (0.93, 1.23)	0.336	1.29 (0.76, 2.20)	0.97 (0.91, 1.05)	0.477	1,092	468,214	1.06 (1.00, 1.13)	0.364	1.00 (0.81, 1.23)	1.01 (0.98, 1.04)	0.525
Loss of ovarian function	63	33,265	1.10 (0.93, 1.31)	0.273	0.91 (0.58, 1.45)	1.03 (0.96, 1.10)	0.391	521	249,676	0.97 (0.89,1.06)	0.997	0.91 (0.73, 1.14)	1.01 (0.98, 1.04)	0.525

Note: The cohorts in this analytic sample were: Breakthrough Generations Study, California Teachers Study, Canadian Study of Diet, lifestyle and Health, Clue II, EPIC, Melbourne Collaborative Cohort Study, Nurses' Health Study I, Nurses' Health Study II, Southern Cmmunity Cohort, US Radiologic Technologists Cohort, Women's Lifestyle and Health Study (Sweden), Black Women's Health Study.

[a] All analyses are stratified by cohort.

[b] p-value for Chi-square test for difference from null model (no BMI term).

[c] HR at age 45 years

[d] Ratio of HR for a one-year change in age-time.

[e] p-value for Chi-square test for difference from constant BMI model.

Table 4
Breast cancer HRs[a] per 5-unit change in BMI by menopausal hormone therapy status.

	Cohorts with information on HRT use							**Restricted to no menopausal hormone therapy**						
			Model 1: Constant BMI		**Model 2: Linear BMI**					**Model 1: Constant BMI**		**Model 2: Linear BMI**		
Menopause status	**n, cases**	**person-years**	**HR (95% CI)**	**p-value[b]**	**linear HR intercept term[c] (95% CI)**	**linear HR term[d] (95% CI)**	**p-value[e]**	**n, cases**	**person-years**	**HR (95% CI)**	**p-value[b]**	**linear HR intercept term[c] (95% CI)**	**linear HR term[d] (95% CI)**	**p-value[e]**
Premenopausal	3,188	1,264,645	0.87 (0.84, 0.91)	0	0.88 (0.83, 0.94)	1.00 (0.98, 1.01)	0.005	1,662	573,545	0.89 (0.85, 0.93)	<0.001	0.92 (0.85, 0.99)	0.99 (0.97, 1.01)	0.644
Hysterectomy without bilateral oophorectomy	153	52,691	0.87 (0.74, 1.03)	0.671	0.97 (0.57, 1.65)	0.98 (0.91, 1.06)	0.756							
Natural	902	417,231	1.05 (0.99, 1.12)	0.992	1.05 (0.83, 1.33)	1.00 (0.97, 1.03)	0.986	420	207,149	1.09 (1.01, 1.18)	0.103	1.00 (0.73, 1.38)	1.01 (0.97, 1.06)	0.019
Loss of ovarian function	473	211,834	1.05 (0.97, 1.14)	0.194	1.07 (0.89, 1.29)	1.00 (0.97, 1.03)	0.924							

[f] Insufficient sample size for estimates restricting to no menopausal hormone therapy.

Note: The cohorts in this analytic sample were: Breakthrough Generations Study, Canadian Study of Diet, Lifestyle and Health, Clue II, EPIC, Melbourne Collaborative Cohort Study, Nurses' Health Study I, Singapore Chinese Health Study, Sister Study, Southern Community Cohort, US Radiologic Technologists Cohort, Black Women's Health Study.

[a] All analyses are stratified by cohort.

[b] p-value for Chi-square test for difference from null model (no BMI term).

[c] HR at age 45 years

[d] Ratio of HR for a one-year change in age-time.

[e] p-value for Chi-square test for difference from constant BMI model.

possibility that the directional change in the BMI HR for breast cancer occurs after age 55 years.

We did not find evidence to support changes over time for the association between BMI and breast cancer risk between ages 45–55 years. To fit within our findings, any proposed mechanisms must take many years to influence risk or initiate after menopause. For example, before menopause, the influence of BMI on hormonal factors such as estrogen and progesterone is one hypothesized mechanism explaining the inverse association between BMI and breast cancer risk [22,23]. Estrogen production shifts from the ovaries to adipose tissue after menopause. This mechanism could support our findings if the change of estrogen production to adipose tissue and its adverse associations with breast cancer risk [24–28] occur gradually after menopause supporting a gradual increase over time without any sudden shift in the association between BMI and breast cancer risk immediately following menopause. A study supporting this mechanism demonstrated a positive association between breast cancer and BMI for a cohort diagnosed after age 60 years, not before [12]. The BMI associated risks for pre- and postmenopausal groups following hormonal changes may begin to diverge in this interval, with the differences persisting, and widening over time, resulting in stronger associations between BMI and risk in older ages.

Our study has some strengths and limitations. First, the consortium, pooling data from many study participants, allowed us to estimate HRs for several postmenopausal groups with more precision than in smaller samples. The enriched concentration of person-time around the age of a typical transition to menopause combined with the large sample size via the consortium, allowed us to evaluate BMI HRs of women who were pre- and peri- menopausal and those who were transitioning beyond menopause.

Limitations are similar to those discussed for the estimation of BMI breast cancer HRs before menopause [6], including the fact that BMI was self-reported for most studies and therefore subject to error. The Sister Study and the Melbourne Collaborative Cohort Study are exceptions because these cohorts provided examiner-based BMI measures at baseline. A previous analysis comparing the self-reported to examiner-based BMI suggested self-reported BMI are reliable for women in the middle BMI range whereas there is a tendency for women with overweight to under-report their weight and women who are underweight to over-report their weight [29]. As discussed regarding this sample and this type of misclassification [6], there could be the potential for bias in estimating the associations between BMI and breast cancer risk and consequently the premenopausal protective association between BMI and breast cancer risk could be closer to 1.0 than what we estimated. However, if this bias is consistent across the age range we examined, this would not impact our findings that assess changes in these associations over age-time. Also, the potential for unbiased estimates to be closer to the null would not change our current findings. Another limitation related to BMI is our approach to carry forward BMI measures if we do not have updated values, which may lead to misclassification. However, in the U.S. BMI for women tends to be quite stable over the interval 45–55 years. Last, BMI may not reflect body fat distribution, which could impact the role of estrogen and adipokines [1].

In summary, among postmenopausal women aged 45–55, the HR for the BMI-breast cancer association was near null, with no evidence of meaningful changes in the HR over age-time within that interval. Among groups of women who were premenopausal or reported hysterectomy without bilateral oophorectomy, the association of BMI with breast cancer risk remained protective with no evidence of changing HRs with age. Evidence supports a near-constant BMI breast cancer HR over age-time during this period among women with natural menopause, suggesting that the transition to BMI breast cancer HRs greater than one reported for postmenopausal women occurs after age 55 years. Factors that may explain this qualitative change are not understood. Future studies should extend to ages beyond 55 years, an age at which almost all women are postmenopausal, to further characterize the dynamics of this change.

Disclaimer

Where authors are identified as personnel of the International Agency for Research on Cancer / World Health Organization, the authors alone are responsible for the views expressed in this article and they do not necessarily represent the decisions, policy or views of the International Agency for Research on Cancer / World Health Organization.

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Declaration of Competing Interest

none.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.canep.2024.102545.

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