

Obesity and the Risk for Premenopausal and Postmenopausal Breast Cancer

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Abstract

Obesity has been consistently associated with an increased risk of postmenopausal breast cancer in population-based studies. Conversely, obesity in such studies has been inversely associated with premenopausal breast cancer risk. In a report of data from two large chemoprevention trials, both of which enrolled women at a high risk of breast cancer, obesity was associated with only a modest, nonsignificantly increased risk of postmenopausal breast cancer and a surprising statistically significant 70% increased risk of premenopausal breast cancer (vs. normal weight). The discrepancies between these results and those from previous observational studies may be due to differences in study design and exposure ascertainment or due to inherent biologic differences whereby the obesity–breast cancer association differs for high-risk women in the clinical setting compared with general population, average-risk women in the observational setting. *Cancer Prev Res*; 5(4); 515–21. ©2012 AACR.

Introduction

A serious consequence of the worldwide obesity epidemic is its implications for cancer incidence and cancer-related mortality (1, 2). One of the most consistent associations of obesity with cancer has been its increased risk for postmenopausal breast cancer. In contrast, in some, but not all studies, obesity has been inversely associated with premenopausal breast cancer. The difference in the direction of the obesity–breast cancer association by menopausal status is a long-standing conundrum and raises questions about whether the etiologies of pre- versus postmenopausal breast cancer differ enough to account for, or whether methodologic differences in design and analysis account for, the consistently contrasting relative risk estimates for obesity. A better understanding of these complex issues will help address etiologic questions and potentially improve public health recommendations for women about their weight and health.

Cecchini and colleagues (3) present data from the large Breast Cancer Prevention Trial (BCPT, or P-1) and Study of Tamoxifen and Raloxifene (STAR) on the association of body mass index [BMI, calculated as measured weight (kg)/height (m²)] with the risk of invasive breast cancer in both pre- and postmenopausal women at a high risk of breast cancer (as reported elsewhere in this issue of the journal).

P-1 tested tamoxifen versus placebo for 5 years in relation to breast cancer risk and included both pre- and postmenopausal women. STAR tested tamoxifen versus raloxifene in relation to the risk of breast cancer and other diseases and included only postmenopausal women. In contrast to many previous reports involving premenopausal women, the P-1 report included multivariate-adjusted HRs for invasive breast cancer of 1.59 [95% confidence interval (CI), 1.05–2.42] for overweight (BMI = 25.0–29.9 kg/m²) and 1.70 (95% CI, 1.10–2.63) for obese (BMI ≥ 30.0 kg/m²) premenopausal women, compared with premenopausal women of normal weight (BMI < 25.0 kg/m²). All models included adjustment for chemoprevention treatment and many standard breast cancer risk factors. There was some evidence to suggest that higher BMI was associated with an increased risk of both estrogen receptor–positive (ER⁺) and ER–negative (ER[–]) disease, although the data for these subgroup analyses were sparse. HRs comparing obese with normal weight premenopausal women were higher among women randomized to tamoxifen (HR, 2.33; 95% CI, 1.10–4.90) than to placebo (HR, 1.41; 95% CI, 0.82–2.43), but the interaction of BMI with treatment group was not statistically significant. The investigators reported a modest, but not statistically significant, increased risk of invasive breast cancer among the overweight and obese postmenopausal women from both trials, which seems to be limited to ER⁺ disease. These results differ from the preponderance of observational evidence showing stronger positive associations of obesity with postmenopausal breast cancer risk.

There is a large body of literature on the relationship of body size with breast cancer risk, dating back at least to the 1960s (e.g., refs. 4, 5). Since 2000, several larger studies, including prospective cohort (6–12) and case–control studies (13–16) and a pooled analysis of 7 prospective cohorts (17), have examined this question in diverse populations

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(Table 1). For premenopausal women, both prospective cohort and case-control studies consistently report a modest (20%–40%) decreased risk of breast cancer in obese women compared with normal weight women, but similar risks for overweight and normal weight women. For postmenopausal women, prospective cohort studies have associated increasing BMI with increasing breast cancer incidence, with some heterogeneity in the strength of this trend. Recent case-control studies in postmenopausal women, however, suggest no relationship between BMI and breast cancer risk (14–16).

Over time, an appreciation for the heterogeneity of breast cancer and its etiology has developed along with larger and more sophisticated study designs and analytic methods, permitting examinations of subgroups of women and breast cancer phenotypes. Because of hypotheses about obesity and aromatase activity, attention has focused on ER status. Stronger inverse BMI-to-risk associations were observed in premenopausal ER⁺/progesterone receptor-positive (PR⁺) cases than in ER⁻/PR⁻ cases (13). Stronger positive BMI-to-risk associations have been reported in postmenopausal ER⁺/PR⁺ cases (9, 10, 14). The limited data available in these studies for other receptor subtypes suggest a null or inverse relationship for both post- (9, 14) and premenopausal (13, 14) women. In recent case-case analyses within a large consortium, obesity was more frequent with receptor (ER and/or PR)-negative than with receptor-positive disease in women ages 50 years old or younger but was more frequent only with PR⁺ tumors in older women (18). Data from the Women's Health Initiative (WHI) revealed similar estimates of the breast cancer risk associated with BMI for ER⁺ and triple-negative (ER⁻, PR⁻, and HER2⁻) cancers (19).

Against this backdrop, the results of Cecchini and colleagues (3) are of particular interest because of the unique setting from which they arise and because findings for both pre- and postmenopausal women challenge the current consensus about the direction of the association in younger women and the magnitude of the effect in older women. Here, we review potential sources of these discrepancies and discuss the implications of these results for our understanding of the obesity-breast cancer association.

Methodologic considerations

Methodologic and study design issues may partly explain why the Cecchini and colleagues (3) results differ from most previous reports indicating inverse associations of obesity with premenopausal breast cancer.

Measurement error in self-reported weight

In the P-1 and STAR trials, height and weight were measured by study staff at baseline, providing objective, reliable measures for calculating BMI before diagnosis. Most other prospective cohort studies also assess BMI at enrollment, but they generally use self-reported height and weight for the assessment. Case-control studies rely on recalled height and weight from a relevant his-

torical timepoint(s) or on postdiagnosis measurements. Although it is generally believed that some agreement exists between objectively measured and self-reported height and weight, population-based studies indicate that reporting a lower-than-actual weight is common with self-assessed weight, particularly among overweight and obese females (20, 21). Nondifferential or random measurement errors, that is, errors that do not depend on true BMI or other participant-specific risk factors, tend to dilute the estimated association of BMI with breast cancer risk relative to the true risk. However, systematic errors in BMI measurements may have the opposite effect, depending on the nature and extent of the measurement error (22). Consideration of both types of errors is important (23). The likely degree of reporting lower-than-actual weight in previous studies, however, cannot account for the difference in magnitude of effect seen between them and Cecchini and colleagues (3), nor does it explain the more important discrepancy in premenopausal women. Therefore, we must look for additional reasons to explain the differences in direction of the obesity-breast cancer relationship by menopausal status.

Timing of the BMI measurement may be an important factor to consider when interpreting these data. Cecchini and colleagues (3) measured BMI only at the time of enrollment in women at least 35 years of age and followed for an average of 4.1 (P-1) or 6.4 years (STAR). Many previous studies collected anthropometry data at various points in life (e.g., at age 18, age 50, and current age) and were able to consider these jointly over extended periods of follow-up. Because obesity may play a much larger role in the elderly (24), differences in the age distribution between studies could explain some of the differences between Cecchini and colleagues and previous studies.

Screening and disease ascertainment

Mammography is the most common means of detecting breast cancer, and its use has been associated with BMI. Obese women are more likely to delay (25, 26), avoid (27), or receive fewer (28) mammography services than are normal weight women, although overweight women obtain mammograms as often as normal weight women (25–27). Overweight and obese women are also more likely to delay clinical breast exams (25, 26). This inverse association seems to be stronger in White than African-American women (25–28). A recent meta-analysis of 17 studies in women 40-plus years old found an inverse association between BMI and mammography use (29). Compared with normal weight women, the ORs for having a mammogram in the 2 years before survey administration were 1.01 (95% CI, 0.95–1.08) for overweight, 0.93 (95% CI, 0.83–1.05) for class I obesity, 0.90 (95% CI, 0.78–1.04) for class II obesity, and 0.79 (95% CI, 0.68–0.92) for class III obesity. Analysis of the largest survey reported to date, however, found that underweight women were considerably less compliant with mammography recommendations than were normal weight women, whereas overweight women reported

Table 1. Reported associations between BMI and invasive breast cancer risk among pre- and postmenopausal women

	BMI, kg/m ²	Premenopausal		Postmenopausal	
		Cases	RR ^{a,b} (95% CI)	Cases	RR (95% CI)
<i>Prospective cohort studies</i>					
Cecchini and colleagues (3), data from 2 large RCTs with BMI measured at baseline and protocol-defined mammography	<25	43	1.00 (ref)	194	1.00 (ref)
	25–29.9	45	1.59 (1.05–2.42)	228	1.07 (0.88–1.30)
	≥30	38	1.70 (1.10–2.63)	331	1.14 (0.94–1.38)
			<i>P</i> = 0.01		<i>P</i> = 0.17
White and colleagues (6), Multiethnic Cohort Study, self-reported baseline BMI, no control for mammography, analysis shown for nonusers of MHT	<20.0			63	0.90 (0.69–1.18)
	20.0–24.9			316	1.00 (ref)
	25–29.9			396	1.35 (1.17–1.57)
	≥30			329	1.60 (1.36–1.87)
					<i>P</i> < 0.0001
Harris and colleagues (7), Nurses Health Study II, a large prospective cohort using self-reported BMI assessed in 1993, no control for mammography	<20.5	132	1.00 (ref)		
	20.6–22.0	128	0.98 (0.76–1.25)		
	22.1–23.9	129	0.94 (0.74–1.20)		
	24.0–27.4	135	0.94 (0.74–1.20)		
	≥27.5	96	0.75 (0.57–0.99)		
			<i>P</i> = 0.03		
Reeves and colleagues (8), MWS—a very large U.K. cohort within a national mammography program, BMI self-reported at baseline; analyses shown among never users of MHT	<22.5	271	0.96 (0.85–1.08)	879	0.85 (0.80–0.91)
	22.5–24.9	352	1.00 (0.90–1.11)	1,336	1.00 (0.95–1.06)
	25–27.4	239	0.93 (0.82–1.05)	1,262	1.10 (1.04–1.16)
	27.5–29.5	151	0.99 (0.84–1.16)	878	1.21 (1.13–1.29)
	≥30	166	0.79 (0.68–0.92)	1,274	1.29 (1.22–1.36)
	Per 10 kg/m ²		0.86 (0.73–1.00)		1.40 (1.31–1.49)
Ahn and colleagues (9), NIH-AARP cohort study using self-reported baseline BMI, no control for mammography, analysis shown for nonusers of MHT	15.0–18.4			6	0.64 (0.28–1.45)
	18.5–22.4			134	1.00 (ref)
	22.5–24.9			179	1.19 (0.95–1.49)
	25.0–27.4			197	1.35 (1.08–1.68)
	27.5–29.9			136	1.52 (1.29–1.94)
	30.0–34.9			175	1.55 (1.22–1.96)
	35.0–39.9			77	1.89 (1.40–2.55)
≥40			44	2.08 (1.44–2.99)	
					<i>P</i> < 0.001
Palmer and colleagues (10), Black Women's Health Study, a large prospective cohort using baseline self-reported BMI, no control for mammography, analyses shown for never users of MHT	<25	157	1.00 (ref)	32	1.00 (ref)
	25–29	169	0.88 (0.71–1.10)	53	0.80 (0.51–1.24)
	30–34	98	0.89 (0.68–1.15)	42	0.88 (0.55–1.42)
	≥35	71	0.72 (0.54–0.96)	38	0.94 (0.58–1.54)
Lahmann and colleagues (11), EPIC, a large multinational European prospective cohort study, BMI measured at baseline, postmenopausal, no control for mammography, results shown among non-MHT users	<21.6	132	1.00 (ref)	98	1.00 (ref)
	21.6–23.5	114	0.95 (0.73–1.23)	127	1.02 (0.78–1.33)
	23.6–25.6	85	0.78 (0.59–1.04)	206	1.35 (1.06–1.73)
	25.7–28.7	75	0.80 (0.59–1.09)	241	1.38 (1.08–1.76)
	≥28.8	68	0.82 (0.59–1.14)	239	1.36 (1.06–1.75)
			<i>P</i> = 0.100		<i>P</i> = 0.002

(Continued on the following page)

Table 1. Reported associations between BMI and invasive breast cancer risk among pre- and postmenopausal women (Cont'd)

	BMI, kg/m ²	Premenopausal		Postmenopausal	
		Cases	RR ^{a,b} (95% CI)	Cases	RR (95% CI)
Morimoto and colleagues (12), WHI observational study, BMI measured at baseline, no control for mammography, analyses shown for never users of MHT	<22.6 >22.6–24.9 >24.9–27.4 >27.4–31.1 ≥31.1			37 54 55 66 103	1.00 (ref) 1.52 (0.95–2.42) 1.40 (0.87–2.32) 1.70 (1.08–2.68) 2.52 (1.62–3.93) <i>P</i> < 0.001
van den Brandt and colleagues (17), pooled analysis of 7 prospective cohort studies, including 2 screening cohorts, BMI self-reported at baseline, no direct control for mammography	<21 21–22.9 23–24.9 25–26.9 27–28.9 29–30.9 31–32.9 ≥33	158 223 131 82 47 32 10 20	1.0 (ref) 1.24 (0.97–1.57) 1.03 (0.78–1.35) 1.08 (0.79–1.48) 0.97 (0.66–1.44) 0.96 (0.60–1.52) 0.55 (0.26–1.15) 0.58 (0.34–1.00) <i>P</i> = 0.007	363 632 699 564 401 224 140 185	1.0 (ref) 1.14 (0.99–1.33) 1.15 (1.00–1.34) 1.26 (1.09–1.47) 1.43 (1.21–1.67) 1.21 (1.01–1.46) 1.29 (1.03–1.60) 1.27 (1.03–1.55) <i>P</i> = 0.001
Case-control studies					
John and colleagues (13), a multi-ethnic case-control study using self-reported and measured BMI collected after diagnosis, no control for mammography	<25 25–29.9 ≥30	298 195 179	1.00 (ref) 0.65 (0.49–0.85) 0.60 (0.45–0.79) <i>P</i> < 0.01		
Berstad and colleagues (14), Women's CARE, a large case-control study in AA and Whites, BMI self-reported 5 years before diagnosis/reference date, no control for mammography	<25 25–29.9 30–34.9 ≥35	1,342 472 168 115	1.0 (ref) 0.92 (0.79–1.08) 0.86 (0.68–1.09) 0.81 (0.61–1.06) <i>P</i> = 0.05	918 579 254 149	1.0 (ref) 0.95 (0.82–1.11) 0.95 (0.77–1.16) 0.96 (0.75–1.24) <i>P</i> = 0.59
Ogundiran and colleagues (15), a case-control study in Nigerian women, BMI measured after diagnosis	<21.0 21.0–23.9 24.0–27.9 ≥28	153 172 170 187	1.0 (ref) 0.89 (0.64–1.24) 0.74 (0.53–1.04) 0.70 (0.50–0.98) <i>P</i> = 0.027	100 115 139 151	1.0 (ref) 1.04 (0.63–1.71) 0.88 (0.55–1.41) 0.76 (0.48–1.21) <i>P</i> = 0.15
Boyd and colleagues (16), nested case-control studies conducted within screened populations using self-reported BMI	≤21.79 21.79–23.30 23.30–25.02 25.02–27.64 >27.64	86 54 49 42 51	1 (ref) 0.69 (0.4–1.1) 0.79 (0.5–1.3) 0.68 (0.4–1.2) 0.76 (0.5–1.3) <i>P</i> = 0.37	159 164 159 170 180	1 (ref) 1.05 (0.8–1.4) 0.95 (0.7–1.3) 1.02 (0.8–1.4) 1.17 (0.9–1.6) <i>P</i> = 0.43

Abbreviations: RCTs, randomized-controlled trials; RR, relative risk; ref, reference (comparator) group; BMI, body mass index; MHT, menopausal hormone therapy; AA, African American.

^aRRs were derived from multivariate proportional hazards models or conditional or unconditional logistic regression models, as reported by each study.

^bAll *P* values associated with RRs are for tests of linear trend with BMI.

slightly higher use of mammography, and the survey found no clear trends with degree of BMI (30). The majority of the studies cited were based on surveys where both BMI and mammography usage were self-reported.

Because higher rates of mammography are associated with increased breast cancer incidence rates (31, 32), differences in mammography use could introduce bias in the association of BMI with breast cancer, as has been observed

for menopausal hormone therapy (MHT), where higher rates of mammography among MHT users likely accounts for part of the differences in risk estimates between observational studies and randomized trials (33). If not accounted for in the design or analysis, less-frequent screening of obese women compared with normal weight women would reduce the corresponding relative risk of disease. Historically, most observational studies have not adjusted for mammography use, and controlling for screening behavior in statistical models is not straightforward (34, 35). An approach reflected by the United Kingdom-based Million Women Study (MWS; ref. 8) is to investigate women within a large screening program. A positive association of BMI with breast cancer risk was seen in postmenopausal women of the MWS, in which women aged 50 to 64 years were invited to screening at 3-year intervals (Table 1). In premenopausal women who were older than 50 years old, however, there was a suggestion of an inverse association, but any reduction in risk was limited to women with a BMI more than 30.0 kg/m².

In the P-1 and STAR trials, concerns about ascertainment bias are minimized by the protocol requirement of regular mammography. Even if differential screening confounded the association of BMI with breast cancer in previous studies, this potential bias does not appear to be large enough to account for the difference between a 20% lower risk of breast cancer for obese premenopausal women in prior observational studies and the 70% increased risk among these women reported by Cecchini and colleagues (3).

Population characteristics

A potential limitation of these analyses within a chemoprevention trial arises from the selection forces inherent in randomized trials. Eligibility requirements for P-1 and STAR yielded by design a much higher risk population than one observes in population-based observational studies. These selection forces were stronger for younger women, who generally needed multiple breast cancer risk factors for eligibility. None of the eligibility factors were directly related to BMI, however, and controlling for them did not change the results substantially. The only other recent study of body size in high-risk women (36) found no statistically significant associations between BMI and breast cancer risk in either pre- or postmenopausal women, although the HRs were consistent in direction with most previous studies.

A noteworthy feature of the P-1 and STAR trial populations is the prevalence of estrogen use among postmenopausal women, reported to be 49% to 54% in P-1 and 69% to 74% in STAR. This prevalence represents a high level of exposure to MHT, which may be important in light of previous observational studies that have reported a significant modification by MHT of the BMI-breast cancer association. In these studies (11, 12, 17), the association between BMI and breast cancer risk was positive in women who were not taking MHT but null among MHT users. If such an effect of hormone use persists beyond the period of exposure, the effect of BMI in postmenopausal women in

the P-1 and STAR trials may be diluted by the persistent effects from MHT. Analyses by White and colleagues (6), however, suggest that the association between BMI and breast cancer risk in former MHT users is similar to that of nonusers. Further, it should be acknowledged that the WHI-randomized trials of MHT did not show a statistically significant interaction between MHT and BMI with respect to breast cancer rates (37–39).

SERM use

Another major difference between Cecchini and colleagues (3) and prior studies is the randomization in P-1 and STAR to selective ER modulators (SERM). The SERMs tamoxifen (used in P-1, STAR) and raloxifene (used in STAR) have a stronger effect on breast cancer risk (40, 41) than does estrogen (38) but are generally thought to work within the same biologic pathway. It is therefore reasonable to consider whether these hormonal prevention strategies modify the BMI association with risk. No evidence of a trend with BMI was seen in postmenopausal women randomized to raloxifene, tamoxifen, or placebo. There also was no interaction between tamoxifen use and BMI for premenopausal women in the P-1 trial.

Potential mechanisms

Several lines of biologic evidence support the positive association of obesity with breast cancer risk. Obesity dysregulates multiple biologic pathways including those related to inflammation, insulin resistance, and endogenous sex hormone synthesis (42, 43). Regarding inflammation, adipose tissue is an active endocrine organ (44) which produces a myriad of cytokines and growth factors, including inflammatory factors, which may in turn induce aromatase (45). People with large adipose tissue stores produce excessive amounts of these compounds, leading to a chronic state of low-level inflammation as well as disturbed regulation of immune function (46) and increased aromatase expression and activity (47), all leading to an increased risk of cancer. We know of no research suggesting that associations of obesity-induced inflammation with breast cancer risk might vary by age or by menopausal status. This mechanism is likely to be consistent across the age continuum and would provide a biologic rationale for the Cecchini and colleagues results (3) among premenopausal women. The association of overweight and obesity with chronic hyperinsulinaemia provides another, perhaps less direct pathway of influence, potentially mediated by insulin receptors in precancerous cells or through secondary changes in hormone metabolism, growth hormones, and insulin-like growth factor 1 (IGF1; ref. 48). None of these pathways alone lends itself to a simple explanation of a differential association of BMI and breast cancer risk in pre- versus postmenopausal women.

The most widely hypothesized biologic mechanism for the BMI association with breast cancer risk relates to the adipose tissue production of estrogen via the aromatization of androgens to estrogens. Postmenopausal women of normal weight have lower levels of endogenous estrogen

than do overweight and obese postmenopausal women, whose levels are elevated as a result of this adipose-derived production. This mechanism presumably accounts for the observation that postmenopausal obesity is more consistently related to ER⁺ than ER⁻ tumors, although as Cecchini and colleagues (3) point out, their and many other studies have too few cases of ER⁻ tumors to definitively rule out obesity-ER⁻ risk associations. Very large cohorts with sufficient numbers of ER⁻ breast cancer cases or collaborative pooling projects of several cohorts may have the power to adequately address these questions.

Summary

Whether obesity is associated with only postmenopausal breast cancer or with both pre- and postmenopausal breast cancer is an important public health issue for the millions of overweight and obese premenopausal women in the United States. The Cecchini and colleagues report (3) used data from 2 large randomized controlled chemoprevention trials, where weight and height were measured with standardized protocols in the proximal interval before diagnosis. This well-conducted study provides important new data suggesting a 50% and 70% increased risk of premenopausal breast cancer for overweight and obese women, respectively. The lack of a strong association of obesity with postmenopausal breast cancer in P-1 and STAR was somewhat

surprising. The reconciliation of these results with previous studies requires consideration of the particular population characteristics in these trials and potential biases in the observational studies.

Many questions remain about the clinical implications of the Cecchini and colleagues results, including questions related to differences in the obesity-breast cancer relationship by tumor phenotype and whether the results of Cecchini and colleagues are relevant for all women or primarily for those at a high risk for breast cancer, as was the case in P-1 and STAR. In conclusion, the clinical and laboratory research communities should carefully consider the important findings of Cecchini and colleagues (3) and consider adding weight reduction and energy balance to the cancer prevention toolbox, at least for women at a high risk for both pre- and postmenopausal breast cancer.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: G.L. Anderson, M.L. Neuhaus.

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