Body Size, Physical Activity, and Breast Cancer Hormone Receptor Status: Results from Two Case-Control Studies[1]

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Abstract

We evaluated whether our previous reports of increased postmenopausal breast cancer risk with higher body mass index (BMI) or of reduced premenopausal and postmenopausal breast cancer risk with higher physical activity levels varied according to the tumor's estrogen receptor (ER) and progesterone receptor (PR) status. Participants enrolled in either of two population-based case-control studies in Los Angeles County, California: one of premenopausal women (ages ≤40 years), and one of postmenopausal women (ages 55–64 years). Case participants were diagnosed for the first time with *in situ* or invasive breast cancer from 7/1/83 through 12/31/88 (premenopausal women) or from 3/1/87 through 12/31/89 (postmenopausal women). Joint ER/PR status was collected for 424 premenopausal and 760 postmenopausal case participants. The analysis included 714 premenopausal and 1091 postmenopausal age-matched, race-matched (white or Hispanic), parity-matched (premenopausal women only), and residential neighborhood-matched control participants.

Among the postmenopausal women, obesity was associated with an increased odds of ER+/PR+ breast cancer (odds ratio, 2.45 for women in the highest *versus* the lowest body mass index quartile; 95% confidence interval, 1.73–3.47). Body mass index was associated with neither ER−/PR− tumors among the postmenopausal women nor with any ER/PR subgroup among the premenopausal women. For both premenopausal and postmenopausal women, higher recreational physical activity levels (≥17.6 MET-hours/week *versus* no activity) were associated with a 30–60% reduction in risk of nearly all ER/PR subtypes, although the associations were generally of borderline statistical significance. Examining these potentially modifiable breast cancer risk factors by tumor ER and PR status may provide us with greater insight into breast cancer etiology and the mechanisms underlying the risk factor associations.

Introduction

The impact of physical activity and body size on breast cancer risk has been evaluated in many recent studies. That these factors may influence breast cancer risk is appealing because they are among the few suspected risk factors amenable to change. Several recent review articles have attempted to characterize the relationship between physical activity, body size, and breast cancer risk (1–4). Although the evidence suggests that each factor has a unique and independent association with breast cancer risk, the factors should not be considered in isolation because of their complex relationship with menopausal status.

Studies of postmenopausal women have consistently reported an increased breast cancer risk associated with obesity, and a number have reported a decreased risk associated with physical activity, even after adjustment for body size. In contrast, studies of premenopausal women have generally reported a lack of or an inverse association of body size and breast cancer risk, but current evidence strongly suggests a reduced breast cancer risk associated with physical activity. A recent review article based on findings from the National Action Plan on Breast Cancer's Workshop on Physical Activity and Breast Cancer (4) suggested that the breast cancer risk reduction associated with physical activity may be greatest among women who are lean, parous, and premenopausal.

Clearly, these findings suggest that physical activity and body size have somewhat different, although possibly interrelated, mechanisms of action. Obesity is hypothesized to increase breast cancer risk of postmenopausal women, in whom the conversion of androstenedione to estrone in body fat results in higher endogenous estrogen levels than in thin women (5–7). This mechanism is biologically unimportant in premenopausal women, whose primary source of estrogen is ovarian and who have estrogen levels that are many fold higher than for postmenopausal women. Physical activity is hypothesized to reduce breast cancer risk by altering the normal cycle of ovulation and menses during the reproductive years and in part by a body size reduction during the postmenopausal years (2).

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ERs[3] are nuclear receptors that bind estrogen, resulting in DNA and protein synthesis, cell division, and breast cell proliferation (8–10). PRs bind progesterone in a similar manner (11). Breast tumors that express ERs and PRs behave differently, both clinically and biologically, than tumors that do not express ERs or PRs (10). Generally, tumors expressing these receptors tend to respond more favorably to hormonal therapies and have a better overall outcome than tumors not expressing ERs or PRs.

Several previous studies have attempted to determine whether tumor subtypes defined by hormone receptor status have different risk factors. Observing that risk factors vary across hormone receptor subtypes would support the hypothesis that hormone receptor status defines biologically unique tumors with different etiologies. On the other hand, observing that risk factors generally do not vary across hormone receptor subtypes would suggest that hormone receptor status does not define biologically unique tumors but rather represents different stages in the continuum of the disease. It is not clear at this point whether body size or physical activity is associated with specific tumor receptor subtypes.

We hypothesized that obesity and lack of physical activity would be associated with increased risk of hormone-responsive tumors (ER+/PR+) but not ER−/PR− tumors, given the hypothesized relation of each factor with endogenous hormone levels. Therefore, to improve understanding of the mechanisms by which physical activity and body size alter breast cancer risk and to provide insight into possible etiological differences between hormone receptor-positive and -negative tumors, we evaluated the relationship of physical activity and body size to the risk of specific breast cancer subtypes defined by hormone receptor status. We present results from two population-based case-control studies conducted in Los Angeles County, California.

Materials and Methods

Participants. The designs of both studies have been detailed previously (12, 13). The methodology for the two studies differed only in the ages of the eligible participants, the time period in which the participants were ascertained, and in one of the variables with which control participants were matched to case patients. In both studies, women were eligible if they were English-speaking, white (including Hispanic), female residents of Los Angeles County, who were born in the United States, Canada, or Western Europe. Eligible breast cancer patients were women consecutively diagnosed with their first primary histologically confirmed *in situ* or invasive breast cancer. In the first study, breast cancer patients were eligible if they were 40 years or younger and diagnosed between July 1, 1983, and December 31, 1988. The second study was restricted to women 55–64 years, with patients diagnosed between March 1, 1987, and December 31, 1989. All patients were identified by the University of Southern California CSP, the population-based cancer registry for Los Angeles County.

We interviewed 744 of the 969 eligible younger ("premenopausal") patients and 1579 of the 2373 eligible older ("postmenopausal") patients. Reasons for nonparticipation were: the physician recommended against contacting the patient (54 premenopausal and 128 postmenopausal patients); the patient refused to be interviewed (111 premenopausal and 419 postmenopausal patients); the patient was too ill or had died (27 premenopausal and 230 postmenopausal patients); the patient had moved out of Los Angeles County and could not be interviewed (12 premenopausal patients); or the patient was lost to follow-up (21 premenopausal and 17 postmenopausal patients).

One neighborhood control participant was individually matched to each of the 744 interviewed premenopausal patients on ethnicity (Hispanic *versus* other white), birthdate (within 3 years) and parity, and to each of 1506 interviewed postmenopausal patients on ethnicity (Hispanic *versus* other white) and birthdate (within 3 years). We were unable to identify and interview an eligible control participant for the remaining 73 interviewed postmenopausal patients.

Control participants were selected from housing units in a predefined walk pattern in the neighborhood where the patient lived at the time of her breast cancer diagnosis. We canvassed each housing unit until a woman who satisfied the case participant-matching criteria was located and interviewed. We made repeated attempts to obtain the information on matching criteria by telephone or mail when no one was home. The first eligible control participant participated for 592 (80%) premenopausal breast cancer patients and for 1205 (76%) postmenopausal patients. The second eligible control participant participated for 124 (17%) premenopausal patients and for 227 (14%) postmenopausal patients after the first eligible control participant refused. We had to identify three eligible control participants for 18 premenopausal and 65 postmenopausal patients, four eligible control participants for 4 premenopausal and 8 postmenopausal patients, five eligible controls for 4 premenopausal and 1 postmenopausal patient, and 7 eligible control participants for 2 premenopausal patients before an interview was obtained. Overall, the response rate among potentially eligible controls was 79% for the study of premenopausal women and 80% for the study of postmenopausal women, based on the total number of women we attempted to recruit to obtain a consenting control participant for each case.

Data Collection. Each study participant completed a face-to-face interview in which she was asked about demographic information, reproductive history, and other known or suspected breast cancer risk factors. For each matched case-control pair and for the unmatched cases, a reference date was created that was the date 12 months before the case's date of breast cancer diagnosis. Information obtained by interview included only those exposures that occurred before the reference date.

Participants provided information about their height, weight, and recreational exercise activities during the structured interview. We queried the participants about their height, their weight in the reference year, their weight at age 18, and their maximum weight (not including times when they were pregnant). BMI, which is a measure of body size, was computed as weight (kg) divided by the square of height (m^2). We created categories of BMI based on the quartile distribution of BMI among the control participants. Adult weight gain was measured as the percentage increase in weight from age 18 to the reference age; for analyses, we used women who experienced weight loss or no weight change as the referent group and created two cut points (three categories) for women who gained weight based on the control participants' distribution.

We queried the participants in both studies about their regular participation (at least 2 h/week) in recreational physical activity. Using open-ended questions, for each activity in which they reported participating regularly, the participant told us the

[3] The abbreviations used are: ER, estrogen receptor; PR, progesterone receptor; OR, odds ratio, CI, confidence interval; BMI, body mass index; CSP, Cancer Surveillance Program.

specific type of activity in which she participated (*e.g.*, aerobics, running, jogging, fencing, tap dance, and others), the age at which she began the activity, the age at which she stopped the activity, and the average number of hours/week that she participated in the activity. If a study participant started and stopped a particular activity more than once, we recorded each period separately. We then computed the average number of hours/week each woman engaged in all recreational physical activities, including seasonal activities, for each year of her life after her first menstrual period. Each recreational activity was assigned a MET value (metabolic equivalents of energy expenditure based on the ratio of kilocalories of energy expended in the given activity to that expended at rest) derived from published tables (14). We then computed average MET-hours/week of recreational physical activity for each year of life from menarche to the reference age. We have published findings previously on the association between physical activity and breast cancer risk for both studies (12, 15).

Exclusions. For the purposes of the analyses, we excluded 11 case patients and 16 control participants from the study of premenopausal women because the women were no longer menstruating, and we excluded 13 case patients and 14 control participants for whom we had no information on family history of breast cancer. After the exclusions, a total of 720 case patients and 714 control participants remained in the study of premenopausal women. We excluded from the physical activity data analysis the first 199 cases and controls enrolled in the study, because the questionnaire was revised to assess lifetime history of regular participation in physical activity subsequent to the enrollment of these participants.

We excluded participants from the study of postmenopausal women if the participants were premenopausal (still menstruating and not using hormone-replacement therapy: 58 case patients and 51 control participants), had an unknown age at menopause (usually hysterectomy without bilateral oophorectomy: 352 case patients and 360 control participants), or did not provide complete information on family history, education, alcohol consumption, pregnancies, breastfeeding, or weight (9 case patients and 4 control participants). After the exclusions, a total of 1160 case patients and 1091 control participants remained in the study of postmenopausal women.

Hormone Receptor Information. We reviewed pathology reports and abstracts collected by the CSP as part of its data collection activities for ER and PR status information (positive *versus* negative) and quantitative ER and PR values, when available, for all of the case patients in both studies. When the CSP reports did not include hormone receptor information, we obtained and examined medical and pathology records from the hospital where the patient was originally diagnosed. For the study of premenopausal patients, we ascertained ER status for 441 (61.3%), PR status for 425 (59.0%), and joint ER/PR status for 424 (59.0%) of the 720 eligible case patients. For the study of postmenopausal women, we ascertained ER status for 805 (69.4%), PR status for 760 (65.5%), and joint ER/PR status for 760 (65.5%) of the 1160 eligible case patients. In both studies, we located the charts, but results of the receptor assays, if done, were not in the record for 50% of women with missing receptor status information; the chart was unavailable, generally because of destruction or hospital closure for about one-third of those missing information; and ER or PR status, but not both, was available for ~10% of the women with missing information.

In both studies, the vast majority of the hormone receptor assays (~85%) were performed using the dextran-coated charcoal method. The cut points for hormone receptor-positive values were those reported by the laboratory that performed the assay. For a very small proportion of the patients in both studies (<2%), cut points for hormone receptor-positive values were either not reported or were reported as borderline. In those cases, we chose the cut point for receptor-positive cases to be 10 fmol/mg for ER and PR, although choosing lower cut points (*e.g.*, 3 fmol/mg) did not materially affect the results. The immunohistochemical method of hormone receptor determination was performed for ~8% of the postmenopausal patients and 3% of the premenopausal patients for whom hormone receptor assays were performed. For these patients, the laboratory provided a written interpretation of the positivity of the result. The method of assay was unknown for ~6% of the postmenopausal and 11% of the premenopausal patients for whom assays were performed. The distribution of breast tumors by joint ER and PR status is shown for each of the studies (Table 1).

Table 1 Distribution of breast tumors by joint ER and PR status in the studies of women 40 years or younger (premenopausal) and of women 55–64 years (postmenopausal), conducted in Los Angeles County, California

ER status	Premenopausal		Postmenopausal	
	PR status		PR status	
	Positive	Negative	Positive	Negative
Positive	209	51	450	159
Negative	19	145	24	127

Statistical Analyses. We evaluated whether the association of body size or physical activity with breast cancer risk varied according to tumor receptor status by computing ORs and 95% CIs within joint ER/PR subgroups using unconditional logistic regression methods. We chose not to retain individual pair matching in the analysis but adjusted for all matching factors. We used four separate models as follows: ER+/PR+, ER+/PR−, ER−/PR−, and ER unknown/PR unknown; each subgroup was compared with eligible control participants. For both studies, there were too few patients with the ER−/PR+ subtype (18 premenopausal and 24 postmenopausal patients) to permit useful analysis. Although we did not to retain the pair matching in the analysis, the results were not materially different when the matching was retained. We examined dose-response effects across categories of a risk factor on a log-linear scale by fitting a coefficient to the median value of each category of a variable. We used polytomous logistic regression analysis to test for heterogeneity in the association of BMI or physical activity across response functions of each joint hormone receptor status subgroup (SAS PROC CATMOD; SAS Institute, Cary, NC).

We conducted separate data analyses for the premenopausal and postmenopausal women. In both sets of analyses, we included matching variables [age at reference year (continuous variable) and socioeconomic status (five categories based on census tract of residence)] in the multivariate models. For the premenopausal study, we also included age at menarche (<12, 12, 13, ≥14 years), age at first full-term pregnancy (never, <20, 20–24, 25–29, ≥30 years), number of full-term pregnancies (none, 1, 2, 3, and ≥4), lifetime months of breastfeeding (none, 1–6, 7–15, ≥16), and first-degree family history of breast cancer (present *versus* absent) in the models.

In the analysis of data from the study of postmenopausal women, we also included number of full-term pregnancies (none, 1, 2, 3, and ≥4), lifetime months of breastfeeding (none, 1–3, 4–6, 7–15, ≥16), age at menopause (<45, 45–49, 50–54, ≥55 years), lifetime months of estrogen-only hormone replace-

Table 2 Multivariate ORs and 95% CIs for anthropometric variables with breast cancer risk according to the joint tumor ER/PR status in the studies of premenopausal and postmenopausal women, conducted in Los Angeles County, California

	Controls	ER+/PR+			ER+/PR−			ER−/PR−			ER unknown/PR unknown		
		Cases	OR	(95% CI)	Cases	OR	(95% CI)	Cases	OR	(95% CI)	Cases	OR	(95% CI)
Postmenopausal[a]													
BMI, reference age													
<21.7	266	71	1.00		34	1.00		31	1.00		90	1.00	
21.7–23.6	277	101	1.36	(0.96–1.94)	38	1.12	(0.68–1.85)	36	1.19	(0.71–1.99)	88	0.95	(0.67–1.36)
23.7–27.0	275	127	1.78	(1.26–2.51)	46	1.35	(0.83–2.20)	25	0.80	(0.45–1.40)	92	1.03	(0.72–1.46)
≥27.1	273	151	2.45	(1.73–3.47)	41	1.29	(0.78–2.15)	35	1.20	(0.70–2.05)	130	1.57	(1.12–2.20)
Trend *P*			0.0001			0.24			0.85[b]			0.009	
BMI, age 18													
<21.7	749	307	1.00		107	1.00		91	1.00		271	1.00	
21.7–23.6	222	96	1.09	(0.83–1.44)	32	0.99	(0.64–1.52)	23	0.85	(0.52–1.38)	89	1.13	(0.84–1.51)
23.7–27.0	83	35	1.02	(0.66–1.55)	17	1.37	(0.77–2.43)	9	0.81	(0.39–1.68)	29	0.94	(0.60–1.49)
≥27.1	37	12	0.75	(0.38–1.49)	3	0.53	(0.16–1.79)	4	0.79	(0.27–2.29)	11	0.77	(0.38–1.56)
Trend *P*			0.82			0.98			0.40			0.77	
% change from age 18 to reference age													
≤0	173	48	1.00		25	1.00		14	1.00		52	1.00	
0.1–14.2	308	104	1.28	(0.86–1.91)	44	1.02	(0.61–1.79)	49	2.12	(1.13–3.99)	104	1.19	(0.80–1.76)
14.3–29.1	303	133	1.71	(1.16–2.52)	51	1.22	(0.73–2.11)	26	1.16	(0.58–2.30)	105	1.22	(0.82–1.81)
≥29.2	307	165	2.32	(1.58–3.41)	39	0.99	(0.58–1.78)	38	1.75	(0.91–3.38)	139	1.71	(1.16–2.53)
Trend *P*			0.0001			0.87			0.61			0.004	
Premenopausal[c]													
BMI, reference age													
<21.7	319	88	1.00		17	1.00		62	1.00		140	1.00	
21.7–23.6	162	54	1.28	(0.86–1.89)	17	2.19	(1.09–4.39)	35	1.11	(0.71–1.77)	64	0.89	(0.63–1.28)
23.7–27.0	115	33	1.03	(0.65–1.64)	11	1.72	(0.77–3.85)	23	0.95	(0.58–1.70)	47	0.80	(0.54–1.21)
≥27.1	118	34	1.11	(0.70–1.77)	6	0.92	(0.34–2.47)	25	1.07	(0.56–1.68)	45	0.80	(0.53–1.20)
Trend *P*			0.68			0.72			0.91			0.20	

[a] Models include age at reference year, socioeconomic status, number of full-term pregnancies, months of breastfeeding, age at menopause, hormone replacement therapy, family history, alcohol consumption, and physical activity.
[b] $0.001 < P < 0.01$ for difference in response function compared with ER+/PR+.
[c] Models include age at reference year, socioeconomic status, age at menarche, age at first full-term pregnancy, number of full-term pregnancies, months of breastfeeding, family history, and physical activity.

ment therapy (none, 1–12, 13–72, 73–120, ≥121 years), lifetime months of combined estrogen and progestin hormone replacement therapy (none, 1–12, 13–72, 73–120, ≥121 years), family history (present *versus* absent), and average grams of alcohol consumed per day (none, 1–13, 14–26, ≥27) in the models. When analyzing BMI, we also adjusted for average MET-hours/week of physical activity from menarche to the reference date (none, 0.1–3.7, 3.8–8.7, 8.8–17.5, ≥17.6). Conversely, for the analyses of physical activity, we adjusted for BMI at the reference date (<21.7, 21.7–23.6, 23.7–27.0, ≥27.1).

Results

We observed a substantially increased risk of ER+/PR+ breast cancer with increasing body size among the postmenopausal women (Table 2). The risk increased in a dose-response manner, culminating in a nearly 2.5-fold relative difference in risk for the heaviest compared with the thinnest women. Risk of ER+/PR− breast cancer was increased slightly among the heaviest women compared with the thinnest, although the relationship was not statistically significant. In contrast to the findings for ER+/PR+ breast cancer, we observed no relationship of BMI to risk of ER−/PR− breast cancer among these postmenopausal participants. BMI at age 18 was not associated with breast cancer risk of any receptor subtype when evaluated using cut points based on quartiles of recent BMI. The results were not different when evaluated using cut points based on quartiles of BMI at age 18 (not shown). We observed no association of BMI with breast cancer risk, overall or by receptor subtype, among the premenopausal participants. In general, for both the premenopausal and postmenopausal studies, results for tumors with unknown receptor type resembled the results for ER+/PR+ tumors, probably reflecting an expected higher proportion of ER+/PR+ than other subtypes among the unknowns.

The association of adult weight change with breast cancer risk appears to be largely restricted to ER+/PR+ tumors (Table 2), for which we observed a marked increased risk associated with increasing weight change from age 18. Adult weight gain was not clearly associated with risk of ER+/PR− or ER−/PR− tumors. We also observed an association of recent body weight with risk of ER+/PR+ tumors only (results not shown).

We found no clear differences in breast cancer risk by ER/PR subgroup when we examined the association of average MET-hours/week of recreational physical activity and breast cancer risk among the postmenopausal women (Table 3). We observed reductions in risk of all ER/PR subtypes for women participating in the highest levels of activity compared with inactive women, although the associations were not statistically significant for either ER+/PR+ or ER−/PR− subtypes.

The premenopausal women had, on average, much greater participation in recreational physical activities than the postmenopausal women. More than 70% of the premenopausal control participants engaged in regular recreational physical activities compared with just over 50% of the postmenopausal control participants. Among the physically active premeno-

Table 3 Multivariate ORs and 95% CIs for physical activity according to joint tumor ER/PR status, in the studies of premenopausal and postmenopausal women, conducted in Los Angeles County, California

Average MET-hours/week from menarche to reference age	Controls	ER+/PR+			ER+/PR−			ER−/PR−			ER unknown/PR unknown		
		Cases	OR	(95% CI)	Cases	OR	(95% CI)	Cases	OR	(95% CI)	Cases	OR	(95% CI)
Postmenopausal[a]													
0	512	227	1.00		85	1.00		65	1.00		209	1.00	
0.1–17.5	494	198	0.92	(0.73–1.16)	67	0.80	(0.56–1.13)	57	0.88	(0.60–1.29)	174	0.82	(0.65–1.05)
≥17.6	85	25	0.69	(0.42–1.13)	7	0.43	(0.19–0.98)	5	0.43	(0.17–1.11)	17	0.50	(0.28–0.87)
Trend *P*			0.16			0.03			0.12			0.01	
Premenopausal[b]													
0	147	52	1.00		11	1.00		40	1.00		77	1.00	
0.1–17.5	273	87	0.85	(0.57–1.28)	21	1.10	(0.51–2.37)	51	0.71	(0.44–1.14)	97	0.69	(0.47–1.00)
≥17.6	102	22	0.60	(0.34–1.07)	7	0.94	(0.34–2.56)	14	0.46	(0.24–0.92)	34	0.61	(0.37–1.02)
Trend *P*			0.09			0.94			0.02			0.03	

[a] Models include age at reference year, socioeconomic status, number of full-term pregnancies, months of breastfeeding, age at menopause, hormone replacement therapy, family history, alcohol consumption, and BMI.
[b] Models include age at reference year, socioeconomic status, age at menarche, age at first full-term pregnancy, number of full-term pregnancies, months of breastfeeding, family history, and BMI.

pausal control participants, 25% averaged at least 19.2 MET-hours/week of activity (equivalent to ~5 h/week of brisk walking or 3 h/week of intensive running) over the time period from menarche to the reference date. We observed a decreased breast cancer risk associated with increasing physical activity levels for both ER+/PR+ and ER−/PR− breast cancers, although we did not observe a significant dose-response trend for the ER+/PR+ tumors (Table 3). For ER−/PR− tumors; however, risk decreased substantially with increasing levels of recreational physical activity, an association that was highly statistically significant. We observed no risk reduction associated with increasing physical activity levels among women with ER+/PR− tumors. The associations of physical activity with ER+/PR+ and ER−/PR− tumors did not appear to vary by age at menarche or parity, but sample size constraints limited the interpretation of these results (not shown).

We examined the interaction of BMI and physical activity among postmenopausal and premenopausal women with ER+/PR+ tumors (Table 4). We were unable to examine adequately the relation among women with other tumor receptor types because of extremely small numbers of women with high levels of physical activity with those receptor types. Overall, we observed no marked variation in the relationship of physical activity with ER+/PR+ breast cancer risk across categories of BMI. Within both high and low categories of BMI, higher levels of physical activity were associated with modest reductions in risk of ER+/PR+ breast cancer.

Discussion

We have reported previously an increased breast cancer risk associated with higher BMI levels in our study of postmenopausal women (15). Our current finding that this association is restricted to women with ER+/PR+ tumors provides further evidence of a hormone-mediated effect of body fat on postmenopausal breast cancer risk. Previous experimental studies have demonstrated the conversion of androstenedione to estrone, the major form of estrogen produced by postmenopausal women, via the aromatase enzyme complex in adipose tissue (5–7). In addition, increased serum levels of free estradiol associated with decreased sex-hormone binding globulin levels and increased triglyceride levels have been demonstrated in obese postmenopausal women (16). Prospective studies of both premenopausal and postmenopausal women have demonstrated an increased breast cancer risk associated with higher endogenous estrogen levels (17, 18).

It remains unclear, however, whether higher endogenous estrogen levels preferentially lead to higher risk of hormone receptor-positive cancers. Only one small prospective study has examined this issue, and the results did not support this hypothesis (19). In this study, investigators collected blood samples and questionnaire data from 7063 postmenopausal women and then followed the women for up to 6 years for the occurrence of breast cancer, resulting in 130 diagnoses. The investigators reported that total estradiol levels and the percentage of free estradiol were generally higher in cases than controls, regardless of ER status. The results for ER-negative tumors were based on only 23 cases, and women were still being enrolled at the time of the last case's diagnosis, suggesting that the follow-up time was very short for some of the cases. It is possible that clinical disease may have been present at the time of blood collection for some of these patients, which may have affected the serum hormone levels. Clearly, there is a need for further investigation in this area.

Our findings for body size are consistent with results reported from a prospective cohort study of over 37,000 55–69-year-old postmenopausal women (20). That study reported a similar association of high BMI with increased risk of ER+/PR+ tumors only, but the cut point for high *versus* low BMI in the prospective study (30.0) was much higher than the cut point for the highest BMI quartile (27.1) in the current study. Of four other studies examining this association in postmenopausal women, the results were mixed. One population-based case-control study (21) and another small case series (22) reported slightly higher mean BMI among women with ER-positive tumors compared with women with ER-negative tumors, differences of borderline statistical significance. The case series also reported statistically significantly higher mean BMI for patients with PR-positive tumors compared with patients with PR-negative tumors. A small hospital-based case-control study reported no difference in any body size indicators with ER-positive compared with ER-negative tumors (23), and a larger case-control study with friend/neighbor controls reported no increased risk of ER+ or ER− breast cancer associated with high body weight (24).

We have reported previously inverse associations between physical activity levels and breast cancer risk in both study

Table 4 ORs and 95% CIs for the interaction of BMI and physical activity, for ER+/PR+ breast tumors in the studies of premenopausal and postmenopausal women, conducted in Los Angeles County, California

BMI	Physical activity[a]	Controls	Cases	OR[b]	(95% CI)
Postmenopausal					
High[c]					
	0	275	148	1.00	
	0.1–17.5	242	115	0.89	(0.66–1.21)
	≥17.6	31	15	0.85	(0.44–1.66)
Low					
	0	237	79	0.57	(0.41–0.80)
	0.1–17.5	252	83	0.54	(0.39–0.75)
	≥17.6	54	10	0.32	(0.15–0.65)
P for interaction				0.61	
Premenopausal					
High					
	0	58	19	1.00	
	0.1–17.5	88	29	0.98	(0.50–1.93)
	≥17.6	25	7	0.86	(0.32–2.34)
Low					
	0	89	33	1.07	(0.55–2.11)
	0.1–17.5	185	58	0.83	(0.45–1.55)
	≥17.6	77	15	0.54	(0.25–1.18)
P for interaction				0.61	

[a] Average MET-hours/week of physical activity from menarche to reference age.
[b] Models include the following: postmenopausal study—age at reference year, socioeconomic status, number of full-term pregnancies, months of breastfeeding, age at menopause, hormone replacement therapy, family history, and alcohol consumption; premenopausal study—age at reference year, socioeconomic status, age at menarche, age at first full-term pregnancy, number of full-term pregnancies, months of breastfeeding, and family history.
[c] High: ≥23.7.

populations reported here (12, 15). We observed a decreased breast cancer risk associated with increasing levels of physical activity for all ER/PR subtypes for both premenopausal and postmenopausal women. Acute as well as sustained physical activity results in many biological changes. It is well established that intense and chronic or sustained physical activity can result in menstrual cycle disturbances including secondary amenorrhea (cessation of menses) and anovulatory menstrual cycles (2). These changes are thought to reduce endogenous estrogen exposure and have been hypothesized to reduce breast cancer risk (25). In addition, physical activity is associated with alterations in immune function, but this relationship is complex and not well understood. In general, moderate levels of physical activity enhance immune function, but highly strenuous physical activity has been shown to depress immune function (2).

Physical activity may also alter breast cancer risk by its effects on body size. However, the associations of physical activity with breast cancer risk defined by hormone receptor status remained, even after adjustment for body size, and did not vary across levels of body size. In addition, if physical activity functioned solely through a reduction in body size, we would not expect to observe a physical activity-breast cancer association in premenopausal women, where body size is not clearly related to risk. Others have examined the interaction of body size and physical activity in relation to breast cancer risk with mixed results. About half of the studies have reported no interaction (12, 26–28), whereas those reporting an association found a stronger physical activity-breast cancer association among thinner women than among heavier women (29–31). These study differences do not appear to be related to either the ages of the participants or the study design. Of the studies reporting no interaction (all case-control studies), two included only very young, mostly premenopausal women (12, 28), one included mostly peri- or postmenopausal women (27), and the other included women with a wide age range (26). Of the studies that noted a stronger association of physical activity with breast cancer risk among leaner women, two (a cohort study and a case-control study) included women of varying ages (29, 30), one (a case-control study) included premenopausal and young postmenopausal women (31), and one (a case-control study) included postmenopausal women only (15).

We found that only recent body size and not body size in young adulthood was associated with risk of ER+/PR+ tumors in postmenopausal women. This finding, combined with the substantial epidemiological evidence of a null or inverse association of body size with premenopausal breast cancer risk (1), suggests that body fat may be acting late in the neoplastic process, possibly by increasing endogenous estrogen levels that fuel the growth of premalignant or early stage ER+/PR+ lesions. In contrast, physical activity was associated with reduced risk of all breast cancer ER/PR subtypes for both premenopausal and postmenopausal women. Physical activity levels were higher in the premenopausal women than in the postmenopausal women, and activity levels in the postmenopausal women declined over time from menarche to 1 year before diagnosis, with most physical activity occurring in the premenopausal years. Perhaps decreased endogenous estrogen levels associated with physical activity reduce proliferation of phenotypically normal breast cells, which may ultimately reduce risk of all breast cancer receptor subtypes.

As with any epidemiological study, the findings from this study should be interpreted in light of study limitations. A potentially important consideration is the substantial difference in the number of participants included in the analyses compared with the original number interviewed, an especially large difference for the postmenopausal study. The bulk of the exclusions in the study of postmenopausal women were women whose age at menopause was unknown; these women were primarily excluded because age at menopause was unknown after a hysterectomy without bilateral oophorectomy. Inclusion of women with unknown age at menopause did not alter the results.

Another consideration is the possibility that risk factor profiles differed between women with and without available receptor status information. However, as we have shown previously (13), the distributions of patient and tumor factors (*e.g.*, ages at diagnosis, menarche, full-term pregnancy, menopause, and number of full-term pregnancies) for both the premenopausal and postmenopausal patients were remarkably similar for patients with and without known tumor hormone receptor status. An important exception was that patients with unknown tumor ER and PR status were much more likely to have been diagnosed with an *in situ* tumor (17% of premenopausal and 23% of postmenopausal patients) compared with women with known ER and PR status (4% of premenopausal and 2% of postmenopausal patients). Because the hormone receptor assays that were most commonly in use when these patients were diagnosed required substantial quantities of tissue, it is likely that patients with *in situ* tumors had insufficient tumor tissue to permit laboratory analysis. We have reported previously that BMI was associated with a slightly lower risk of *in situ* compared with invasive breast cancer for both premenopausal and postmenopausal women (32). When we repeated our current physical activity and BMI analyses after excluding patients with *in situ* tumors, we observed no material differences in our results, as expected given the relatively small proportion of patients with *in situ* tumors and known ER and PR status

(results not shown). We had also observed that patients with unknown ER and PR status were somewhat more likely to have had a family history of breast cancer (19% of premenopausal and 21% of postmenopausal patients) compared with patients with known ER and PR status (11% of premenopausal and 17% of postmenopausal patients). However, when we restricted the analysis to patients without a family history of breast cancer, the results for both physical activity and BMI were not materially different (not shown).

As with any case-control study based on self-report, it is possible that the case participants may have recalled certain exposures differently than control participants, especially for exposures widely thought to be associated with breast cancer. However, both case-control studies were conducted in the 1980s when the relationships between physical activity, body size, and breast cancer risk were largely unknown and newly under investigation. It is therefore unlikely that the case participants would have either underreported their activity levels or overreported their body weights relative to the control participants because of prior knowledge of an association of either of these factors with breast cancer risk.

This study provides further clues into the mechanisms underlying the associations of body size and physical activity with breast cancer risk, and it provides a glimpse into the etiology of hormone receptor-positive and -negative cancers related to these breast cancer risk factors. However, many questions remain unresolved. It is unclear at what point in the neoplastic process hormone receptor attributes arise. It is also unclear whether high endogenous estrogen levels induce estrogen receptors during tumor development or if they fuel proliferation of early hormone receptor-positive lesions. Further research into tumor hormone receptor determinants and the natural history of hormone receptor development will provide clues into the causes underlying the development of breast cancer and will help elucidate more effective breast cancer preventive measures.

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