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EFFECT OF FAMILY HISTORY, OBESITY AND EXERCISE ON BREAST CANCER RISK AMONG POSTMENOPAUSAL WOMEN

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We examined effects of obesity and lifetime exercise patterns on postmenopausal breast cancer risk according to family history in a large population-based case control study conducted in Los Angeles County, California, because we hypothesized that both factors would affect risk through similar mechanistic pathways, and that their effects would be stronger among women with a family history. We studied 1,883 postmenopausal breast cancer case subjects and 1,628 postmenopausal control subjects ranging in age from 55–72 years. Cases were diagnosed with incident breast cancer in the late 1980s and 1990s. Controls were individually matched to case subjects on age, ethnic origin and neighborhood. In-person interviews determined known breast cancer risk factors including: height, weight, lifetime exercise, and family history of breast and other cancers. Breast cancer risk was raised among women who had at least 1 first-degree relative with breast cancer (odds ratio [OR] = 1.68; 95% confidence interval [CI] = 1.36–2.08). Risk increased with increasing levels of body-mass index (wt-kg/ht-m^2) (p-trend = 0.005). Breast cancer risk was reduced among women who maintained, on average, 17.6 metabolic equivalent of energy expenditure (MET)-hr of activity/week from menarche onward (OR = 0.66; 95% CI = 0.48–0.90). Body-mass index, adjusted for lifetime exercise, was strongly associated with breast cancer risk among women with a positive family history of breast cancer (p-trend < 0.0001), but only weakly associated among women with no family history (p-trend = 0.08; homogeneity of trends p = 0.0005). In contrast, the risk reduction associated with exercise activity, adjusting for body-mass index, was limited to women without a family history of breast cancer (p-trend = 0.001; homogeneity of trends p = 0.005). Body-mass index and exercise activity, both modifiable risk factors for breast cancer, seem to have differential effects depending on a woman's family history of breast cancer, and may impact risk through different biological mechanisms.

Key words: *breast neoplasms; family history; obesity; exercise*

Family history is often used to help identify disease-related genetic factors.[1] In early studies, family history was an important clue that led investigators to localize young onset familial breast cancer to chromosome 17q21,[2] and ultimately to identify the BRCA1 gene.[3]

Family history, however, probably represents more than major gene effects. Among women with 1 or 2 first-degree relatives with breast cancer (moderate-risk families), family history remains a predictor of breast cancer risk after statistically accounting for the expected effects of BRCA1 and BRCA2 gene mutations.[4] Other factors such as unidentified mutations in other genes or familial aggregation of environmental or behavioral risk factors may be responsible for the residual effect of family history.[5]

Obesity and weight gain as an adult are associated with increased breast cancer risk after menopause.[6,7] Several mechanisms have been proposed to account for this increased risk including the conversion of the adrenal androgen, androstenedione, into estrone through aromatization that occurs in body fat,[8] a decrease in sex-hormone binding globulin (SHBG) levels resulting in higher levels of circulating bioavailable estrogen,[9] an increase in insulin levels[10] or a combination of these factors.

Exercise activity has been studied extensively in relation to breast cancer risk, with many large case-control and cohort studies finding protective effects.[11–16] Exercise activity may protect premenopausal women by reducing exposure to ovarian hormones,[17] and postmenopausal women by maintaining or lowering body weight in addition to exerting independent effects on estrone levels.[14,18]

We examined previously the effects of lifetime exercise and weight change on breast cancer risk in the first phase of a case-control study of postmenopausal women.[14] That report was based on 1,123 cases and 904 controls. We now examine the effects of obesity and exercise according to family history of breast cancer in the completed study of 1,883 cases and 1,628 controls.

MATERIAL AND METHODS

Selection of subjects

All breast cancer cases were identified by the Cancer Surveillance Program (CSP), the population-based cancer registry for Los Angeles County. Group I breast cancer patients were diagnosed between March 1, 1987–December 31, 1989. Eligible women were Caucasian (including Hispanic-Caucasian), born in the United States, Canada or Western Europe; and between the ages of 55–64 years at diagnosis. We reported on these subjects previously.[14] Group II patients diagnosed between January 1, 1992–December 31, 1992, were Caucasian (including Hispanic-Caucasian), or African-American, born in the United States, and between the ages of 55–69 years at diagnosis. Group III patients were diagnosed between September 1, 1995–April 30, 1996, were Caucasian (including Hispanic-Caucasian) or African-American, born in the United States, and were between the ages of 55–72 years at diagnosis. This data collection sequence was adopted to optimize our ability to study the relationship between hormone replacement therapy and breast cancer, the principal goal of the study.[19] Interviews

Cancer incidence data have been collected under Subcontract 050L-8709-S1149 with the Contractor, Public Health Institute. The subcontract is supported by the California Department of Health Services as part of its statewide cancer-reporting program mandated by Health and Safety Code Sections 103875 and 103885.

The ideas and opinions expressed herein are those of the authors and no endorsement by the State of California, Department of Health Services, or the Contractor is intended or should be inferred.

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were completed within 1 year of diagnosis for 2,653 of the 3,976 eligible patients. Eligible patients were not interviewed for the following reasons: physicians refused permission to contact 144 patients (4%); 794 patients refused to participate (20%), and 385 patients died or were too ill to participate (10%).

We individually matched 1 control subject to each breast cancer patient by age (within 3 years), ethnic origin, and neighborhood of residence.[19] To identify each neighborhood control subject, we utilized predefined walk patterns for neighborhoods where case patients lived at the time of diagnosis. Matched control subjects were interviewed for 2,429 patients (see Ross *et al.*[19] for more detail); no matched control subject was found for 224 patients (9%). The first qualifying control subject refused to participate in 536 instances (22%) and an additional matched control subject was sought. Median number of households approached per case patient was 33.

Study procedures to protect human subjects were approved by the federally designated University of Southern California Institutional Review Board, in accord with assurances approved by the U.S. Department of Health and Human Services. Each subject provided informed consent.

Data collection

Interviews for each case-control pair were generally conducted by the same female interviewer. We obtained lifetime reproductive, oral contraceptive, hormone replacement therapy and physical exercise histories. We recorded exposure information up to a reference date (12 months before the date of the patient's diagnosis for each case and her matched control). A woman had a first-degree family history of breast cancer if her mother or sister had been diagnosed with breast cancer. We recorded self-reported height and weight at age 18 years and at the reference date. An index of body mass was estimated as weight in kilograms divided by the square of height in meters. We calculated percent change in weight between age 18 and the reference date. Women who lost or had no weight change constituted the referent category. The remaining distribution of weight change was divided into three groups according to whether subjects were below the 50th centile value, below the 75th centile, or above the 75th centile of control subjects.[14]

We collected lifetime histories on exercise activity where duration of activity was at least 2 hr/week for 1 year. We recorded type of activity, ages started and stopped, and number of hr/week spent exercising. For each year of life, we computed total hr/week spent on all exercise activities. In addition, we assigned a score based on metabolic equivalents of energy expenditure (METs) to each activity,[20] calculated MET-hours for each activity, and summarized the MET-hour values across all activities for each year of life.

We constructed several physical activity variables as described previously.[14] Variables included average MET-hours/week over the woman's lifetime (from menarche to her reference date), number of years a woman exercised more than 4 hr/week (from menarche to reference date), and average MET-hours of exercise/week in the 10-year period before the woman's reference date. For each variable, the referent group was inactive women.

Data analysis

Statistical analyses were limited to postmenopausal women with known ages at menopause and complete covariate information (1,883 cases, 1,628 controls). We excluded the following: women with unknown age at menopause (n = 1,136 primarily women who underwent a hysterectomy without oophorectomy); menstruating women (n = 171); women with last menstrual period before their 35th birthday (n = 52); women with missing covariate information (n = 62) including 20 women who were adopted or did not know their first degree family history of breast cancer; and controls with ages outside the age range of the cases, <55 years or >72 years (n = 146).

Because these exclusions affected our case-control matching, we constructed conditional logistic models using a stratified analytic approach. We created strata according to age at reference date (2 year age groups), year of birth (2 year groupings), socioeconomic status assigned to census tract of residence (average education and income levels in the census tract: 4 categories ranging from low to high), and ethnicity groupings (non-Hispanic Caucasian, Hispanic Caucasian and Black). This analytic strategy, which resulted in 326 strata, differed from that used in our first publication of Group 1 subjects.[14] We applied the matching strategy from our earlier publication and reanalyzed our data; the risk estimates were similar to those presented here.

We estimated odds ratios (OR), 95% confidence intervals (CI) for the OR (based on SE of the log odds), and tests for linear trend across ordinal values of categorical variables by conditional logistic regression methods, using the statistical package program, EPILOG (Epicenter Software, Pasadena).[21] All conditional logistic regression models included terms for age at menarche (<12, 12, 13, >13), age at menopause (35–39, 40–44, 45–49, 50–54, ≥55), age at first term pregnancy (<20, 20–24, 25–29, 30–34, ≥35, nulliparous) and interviewer. Models were additionally adjusted for family history of breast cancer in mother or sister(s) (no, yes), body-mass index at reference date (<21.7, 21.7–23.6,23.7–27.0, ≥27.1), and lifetime exercise (0, >0–3.74, 3.75–8.74, 8.75–17.59, ≥17.6 MET-hr/wk), except in situations where one of the risk factors in question was being evaluated. Adjustment for total months of HRT usage did not alter the risk estimates. In addition, evaluating the effects of body-mass index, adulthood weight change, and exercise among non-users and users of HRT simultaneously did not produce appreciably different risk estimates. Therefore HRT was not included in models presented here. All p-values reported are 2-sided. To assess effect modification by family history of breast cancer, we constructed a likelihood ratio test that compared 2 logistic models, 1 with a single trend variable for exercise activity (or body mass index) and the other with 2 trend variables, 1 for women with a positive family history and the other for women with a negative family history (test for homogeneity of trends).

RESULTS

Breast cancer risk was elevated among women with at least 1 first degree-relative who had breast cancer (OR = 1.68; 95% CI = 1.36–2.08) (Table I). Women whose mother was the sole family member diagnosed with breast cancer had a 52% greater risk of breast cancer than did women with no family history (OR = 1.52; 95% CI = 1.15–2.01). Women with an affected sister (or sisters) had a moderately higher risk (OR = 1.82; 95% CI = 1.32–2.50). Risk was highest among women with both a mother and at least one sister with breast cancer (OR = 2.57; 95% CI = 0.98–6.70).

We retained exercise and anthropometric cutpoints of our earlier publication[14] to evaluate whether addition of the remaining study participants had impacted our previous observations. Breast cancer risk increased with increasing levels of body-mass index at reference date (p-trend = 0.005), but body-mass index at age 18 was unrelated to risk (p-trend = 0.74) (Table II). Women in the upper level of body-mass index (>27.1 kg/m^2) had 1.34 greater odds of developing breast cancer than women in the lowest level (<21.7 kg/m^2, OR = 1.34; 95% CI = 1.09–1.66). Women who experienced the greatest percent weight gain between age 18 and the reference age (>29.2%) were similarly at increased risk (OR = 1.36; 95% CI = 1.08–1.73). Height was unrelated to breast cancer risk (p-trend = 0.80). We evaluated the body-mass index effect divided according to clinical guidelines for overweight and obesity.[22] Overweight (body mass index: 25–29.9) and obese (body mass index ≥30) women had OR of 1.14 (95% CL = 0.96–1.36) and 1.22 (95% CL = 0.99–1.50) as compared to women at normal weight (body mass index <25) (data not shown).

Breast cancer risk was reduced among women who maintained, on average, 17.6 MET-hours of activity/week from menarche to reference date (OR = 0.66; 95% CI = 0.48–0.90), compared to

TABLE I – ADJUSTED ODDS RATIOS AND 95% CONFIDENCE INTERVALS FOR BREAST CANCER AMONG WOMEN WITH A FIRST DEGREE RELATIVE WITH BREAST CANCER

Variable	Cases	Controls	OR (95% CI)[1]
First degree family history of breast cancer			
No	1,567	1,449	1.00 —
Yes	316	179	1.68 (1.36–2.08)
Type of family history[2]			
No	1,567	1,449	1.00 —
Mother only	155	99	1.52 (1.15–2.01)
Sister (at least 1) only	143	74	1.82 (1.32–2.50)
Mother and at least one sister	18	6	2.57 (0.98–6.70)

[1]Adjusted for lifetime exercise activity, age at first term pregnancy, age at menarche, age at menopause, and body-mass index at reference age.–[2]All family history categories are mutually exclusive.

TABLE II – ADJUSTED ODDS RATIOS AND 95% CONFIDENCE INTERVAL FOR BREAST CANCER RISK BY ANTHROPOMETRIC MEASURES AND PHYSICAL EXERCISE ACTIVITY

Variable	Cases	Controls	OR(95% CI)	Trend (*p*-value)
Body-mass index[2] at reference date[3,4]				
<21.7	366	370	1.00 —	
21.7–23.6	379	355	1.10 (0.88–1.37)	
23.7–27.0	497	439	1.18 (0.95–1.46)	
≥27.1	641	464	1.34 (1.09–1.66)	0.005
Body-mass index[1] at age 18[4]				
< 18.9	475	406	1.00 —	
19.0–20.29	418	373	0.88 (0.71–1.08)	
20.3–22.16	538	447	1.03 (0.84–1.25)	
≥ 22.17	452	402	0.91 (0.74–1.13)	0.74
Height at age 18 (inches)[5]				
< 62	274	254	1.00 —	
62–63	467	433	0.93 (0.73–1.18)	
64–65	580	470	0.99 (0.78–1.26)	
≥ 66	562	471	0.94 (0.99–1.20)	0.80
Change in weight from age 18 to reference date (%)[4]				
Negative change to no change	229	247	1.00 —	
>0–16.9	573	512	1.16 (0.92–1.47)	
17.0–29.1	404	359	1.13 (0.88–1.45)	
≥ 29.2	677	510	1.36 (1.08–1.73)	0.01
Lifetime exercise between menarche and reference date (average MET-hours per week)[6]				
0	958	773	1.00 —	
>0–3.74	400	371	0.85 (0.71–1.03)	
3.75–8.74	217	201	0.87 (0.69–1.10)	
8.75–17.59	207	166	1.02 (0.79–1.30)	
≥17.6	101	117	0.66 (0.48–0.90)	0.07
Years engaged in more than 4 hours per week of exercise activity[6,7]				
0	1358	1098	1.00 —	
>0–5	167	187	0.78 (0.62–1.01)	
6–11	159	143	0.90 (0.69–1.17)	
≥12	199	200	0.76 (0.60–0.96)	0.01
Average exercise activity in 10 years prior to reference date[6,8] (average MET-hours per week)				
0	1,288	1068	1.00 —	
>0–6.9	153	134	0.93 (0.71–1.22)	
7.0–13.9	173	141	0.92 (0.70–1.19)	
14.0–24.4	153	155	0.86 (0.65–1.11)	
≥24.5	116	130	0.75 (0.55–1.02)	0.05

[1]Adjusted for age at first full-term pregnancy, ages at menarche and menopause, family history of breast cancer, and interviewer.–[2]Weight (kg)/height^2 (m).–[3]One year prior to breast cancer diagnosis for cases and corresponding date for controls.–[4]Additionally adjusted for average MET hours per week of lifetime exercise activity.–[5]Additionally adjusted for weight (lb.) at reference date.–[6]Additionally adjusted for body-mass index at reference date.–[7]Additionally adjusted for number of years in which the average amount of exercise was 4 hr per week or less.–[8]Additionally adjusted for average MET-hours per week of exercise to 10 years prior to reference date.

inactive women (Table II). Similar to the results reported previously, average MET-hours of activity/week in the 10-year period before the reference date was modestly associated with a reduction in risk among women who averaged at least 24.5 MET-hours of exercise activity/week (OR = 0.75; 95% CI = 0.55–1.02). Women who exercised more than 4 hr/week for 12 or more years were 24% less likely to develop breast cancer than women who never exercised at that level (OR = 0.76; 95% CI = 0.60–0.96).

We examined whether family history of breast cancer modified effects of body size on breast cancer risk (Table III). Among women with a first-degree family history of breast cancer, body-mass index at reference date was strongly associated with an increased risk of breast cancer (p-trend < 0.0001). Among women in the upper level of body-mass index, risk was 2.9 times greater than that of women in the referent level (OR = 2.90; 95% CI = 1.86–4.54). Height, independent of body-mass index, was mod-

TABLE III – ADJUSTED ODDS RATIOS AND 95% CONFIDENCE INTERVALS FOR BREAST CANCER ASSOCIATION WITH ANTHROPOMETRIC MEASURES AND EXERCISE ACTIVITY AMONG POSTMENOPAUSAL WOMEN WITH AND WITHOUT A FAMILY HISTORY OF BREAST CANCER

Measure	Category	Family history of breast cancer							
		No family history				Positive family history			
		Cases/ controls	OR	(95% CI)	Trend (p-value)	Cases/ controls	OR	(95% CI)	Trend (p-value)
Body-mass index at reference date[1,2]									
< 21.7		312/333	1.00	—		54/37	1.00	—	
21.7–23.6		311/303	1.06	(0.84–1.33)		68/52	1.48	(0.97–2.25)	
23.7–27.0		404/389	1.11	(0.89–1.39)		93/50	1.76	(1.18–2.61)	
≥ 27.1		540/424	1.20	(0.97–2.19)	0.08	101/40	2.90	(1.86–4.54)	<0.0001
Homogeneity of trends p-value					0.0005				
Percent change in weight from age 18 to reference date[1,2]									
Negative change to no change		191/225	1.00	—		38/22	1.00	—	
>0–16.9%		475/436	1.17	(0.92–1.48)		98/76	1.28	(0.88–1.85)	
17.0–29.1%		335/319	1.05	(0.81–1.36)		69/40	1.86	(1.16–2.97)	
≥ 29.2%		566/469	1.22	(0.96–1.55)	0.21	111/41	3.03	(1.95–4.71)	<0.0001
Homogeneity of trends p-value					<0.0001				
Height at age 18 (inches)[1,3]									
< 62		227/230	1.00	—		47/24	1.00	—	
62–63		396/383	0.87	(0.67–1.12)		71/50	1.40	(0.90–2.18)	
64–65		483/425	0.92	(0.72–1.18)		97/45	1.77	(1.14–2.72)	
≥ 66		461/411	0.90	(0.70–1.16)	0.64	101/60	1.29	(0.87–1.92)	0.04
Homogeneity of trends p-value					0.025				
Lifetime exercise between menarche and reference date[2,4]									
0		801/689	1.00	—		157/84	1.00	—	
>0–17.59		683/657	0.83	(0.71–0.97)		141/81	1.44	(1.05–1.99)	
≥ 17.6		83/103	0.63	(0.45–0.89)	0.001	18/14	0.85	(0.40–1.79)	0.15
Homogeneity of trends p-value					0.005				
Years engaged in more than 4 hours per week of exercise activity[5]									
0		1125/977	1.00	—		233/121	1.00	—	
>0–11		275/296	0.78	(0.57–0.93)		51/34	1.32	(0.81–2.15)	
≥ 12		167/176	0.73	(0.57–0.93)	0.002	32/24	0.94	(0.52–1.63)	0.75
Homogeneity of trends p-value					0.10				
Average exercise activity in 10 years prior to reference date (average MET-hours per week)[2,6]									
0		1072/955	1.00	—		216/113	1.00	—	
>0–6.9		130/114	0.93	(0.70–1.24)		23/20	0.93	(0.47–1.86)	
7.0–13.9		135/123	0.84	(0.63–1.11)		38/18	1.50	(0.81–2.79)	
14.0–24.4		126/142	0.74	(0.56–0.98)		27/13	1.96	(0.94–4.10)	
≥ 24.5		104/115	0.72	(0.53–0.97)	0.003	12/15	0.75	(0.33–1.70)	0.27
Homogeneity of trends p-value					0.025				

[1]Adjusted for age at first full-term pregnancy, age at menarche, age at menopause, interviewer, and lifetime exercise activity.–[2]Reference date defined as 1 year prior to breast cancer diagnosis for cases and corresponding date for controls.–[3]Adjusted for categories of weight at reference date.–[4]Adjusted for age at first term pregnancy, age at menarche, age at menopause, interviewer, and body-mass index at reference date.–[5]Additionally adjusted for continuous term for number of years in which average amount of exercise was 4 hr per week or less.–[6]Additionally adjusted for continuous term for average MET hours up until 10 years prior to reference date.

estly associated with risk among women with a family history of breast cancer (p-trend = 0.04). Among women without a family history of breast cancer, body-mass index at reference age was weakly associated with breast cancer risk and height was not associated with risk.

Body-mass index divided according to clinical guidelines was also more strongly associated with breast cancer risk among women with a positive family history. Odds ratios for overweight women were 1.83 (95% CI = 1.22–2.73) and for obese women were 2.78 (95% CI = 1.58–4.88), compared to women with normal weights (data not shown).

We evaluated adult weight change according to family history. Among women with a positive family history, gaining more than 29.2% of weight relative to weight at age 18, was strongly associated with risk (p-trend < 0.0001). Comparing the linear trends in risk of women with a family history of breast cancer to those without, the results indicated a marked difference for the trends in risk associated with body-mass index at reference date (homoge-

neity of p-trends = 0.0005) and adult weight gain (homogeneity of p-trends < 0.0001), and a modest difference in trends for height (homogeneity of p-trends = 0.025).

We also evaluated lifetime exercise activity according to family history of breast cancer, adjusting for body-mass index (Table III). Risk reductions associated with exercise activity were largely limited to women who had no family history of breast cancer. For example, women with a negative family history who had exercised, on average, more than 17.6 MET-hr/week since menarche had a 37% reduction in risk compared to sedentary women (OR = 0.63; 95% CI = 0.45–0.89). The reduction in risk for women with a positive family history who exercised at that same level was smaller (OR = 0.85; 95% CI = 0.40–1.79). Similar patterns were observed for years of exercise that exceeded 4 hr/week, and exercise that occurred in the 10-year period before the reference age. For lifetime activity and activity in the past 10 years, trends in risk for women with and without a family history of breast cancer differed significantly (p = 0.005 and p = 0.025, respectively).

We constructed an 8-level variable with no family history and the lower category of body-mass index as the referent group. Among women in the upper category of body-mass index with a positive family history compared to women in the lowest category without a family history, the OR was 3.05 (95% CI = 1.94–4.79). We repeated the same procedure for percentage weight change and observed similar results. Women with a positive family history who gained more than 29.2% of weight during adulthood (relative to weight at age 18 years) had an OR of 3.36; (95% CI = 2.15–5.26).

DISCUSSION

We first became interested in the role of hormones, especially estrogens, in the familial risk of breast cancer several decades ago when our epidemiology colleagues demonstrated that serum levels of estrone and estradiol are higher among daughters of patients with breast cancer, than age-matched control women.[23] Begg *et al.*[24] showed that serum-levels of estrone, independent of body-mass, are higher among postmenopausal sisters of women with breast cancer than among sisters of controls. Interestingly in the same study, sisters of breast cancer patients also weighed significantly more than control sisters. These observations suggested to us that modifiable risk factors for breast cancer that are likely to be mediated through hormonal pathways, might have differential effects depending on a woman's family history of breast cancer.

Conversion of androstenedione to estrone in adipose tissue, the primary source of estrogen after menopause, is regarded widely as the most likely mechanism to explain the increased risk of post-menopausal breast cancer among obese women. Larger amounts of adipose tissue increase circulating estrone levels in proportion to the amount of adipose tissue.[25] Estrone is converted to estradiol, a more potent estrogen. Combined data from nine prospective studies that evaluated endogenous hormones and breast cancer risk among postmenopausal women documents that risk is elevated with increasing levels of each of these hormones: androstenedione, estrone and estradiol.[26] For each hormone, the breast cancer risk of post-menopausal women in the quintile of highest hormone concentration is roughly 2 times greater than that of women in the lowest quintile. Obesity is also associated with lower circulated levels of sex-hormone binding globulin (SHBG), a protein that binds and inactivates estradiol, resulting in increased bioavailable fractions of estrogens.[9]

Other mechanisms may also account for the relationship between obesity and breast cancer risk. Obese postmenopausal women have increased circulating insulin levels.[27] Insulin stimulates the growth of breast-cancer cell lines,[27] and may increase breast cancer risk.[10,28] Insulin-like growth factors (IGFs) are peptides that help regulate tissue growth and fat deposition. One of these, IGF-1, stimulates mitosis in breast cancer cells.[29] IGF-1 levels may be higher among obese women,[30] and some epidemiologic studies have found that IGF-1 levels are associated with increased risk of breast cancer in premenopausal but not in post-menopausal women.[31,32]

Likewise, exercise is thought to reduce postmenopausal breast cancer risk indirectly by promoting weight loss and, more directly, by affecting hormone and growth factor levels. Postmenopausal women who exercise have lower circulating levels of estrone, and this relationship seems to be independent of body mass.[18] Increased levels of exercise are associated with elevated circulating concentrations of SHBG,[33] enhanced insulin sensitivity[34] and reduced plasma levels of insulin.[35] In addition, exercise may down-regulate bioavailable IGF-1 through increased production of one of its binding proteins, IGFBP-3.[36]

We evaluated lifetime exercise activity and obesity according to family history of breast cancer expecting to find that if effects differed by family history, these differential effects would be comparable for both exercise and obesity because there are several common pathways by which these factors might modify breast cancer risk. Our findings that exercise impacts women without a family history and obesity impacts those with a family history suggest that either these 2 important risk factors might affect breast cancer risk through different mechanistic pathways or that one pathway might predominate to a greater extent for obesity than for physical exercise activity, depending on family history.

Our epidemiology colleagues developed the concept that hormonal breast cancer risk factors can explain breast cancer incidence based on their impact on circulating estrogen levels and, in turn, on their effect on breast epithelial cell proliferation.[37] The magnitude of the effect of obesity on breast cancer risk of women with first degree family history of breast cancer that we observed in our study would seem to be greater than anticipated based on the impact of excess body fat on circulating estrogen levels given the small increase in risk observed among women without a family history. It is plausible that more extensive local aromatization of androstenedione to estrone occurs among women with a positive family history, or that the presence of mutated forms of certain breast cancer susceptibility genes increases sensitivity of breast cells to estrogen stimulation.

Previous studies that have evaluated whether family history of breast cancer modifies the effect of obesity on postmenopausal breast cancer risk have reported mixed results.[7,38,39] A pooled analysis of existing prospective cohort studies found no interaction for effects of body-mass index and family history on breast cancer risk;[7] 1 case-control study found moderate effect modification with weight change since age 18;[38] and 1 prospective study of post-menopausal women found stronger effects for waist-to-hip ratio on breast cancer risk among women with a positive family history.[39] The dissimilar results observed may be due to different methods of eliciting anthropometric measures as well as the unequal distribution of pre and postmenopausal women among the study populations. The pooled analysis and case-control study included both pre- and postmenopausal women, whereas the prospective cohort study followed women who were ages 55–69 years at recruitment. The case-control study relied on telephone interviews to elicit risk factor information; the pooled analysis and prospective study were based on self-administered questionnaires.

Prior studies of family history and exercise also show inconsistent results. A study that found only modest non-significant protective effects of exercise on postmenopausal breast cancer risk overall did not show any differential association between exercise and breast cancer risk by family history.[39] The study measured recreational exercise at 2 ages; young adulthood and middle age. In contrast with our findings, a study of lifetime exercise effects on the breast cancer risk of mostly premenopausal women, which noted substantial protection overall, found the protection stronger for women with a positive family history.[15] Quite possibly differing results of exercise activity according to family history across studies may also depend upon menopausal status, and different methods for eliciting information about exercise activity.

Our study has several potential limitations. Obese women may have systematically underreported their weight; if this underreporting were more extreme in control subjects than case patients, we would overestimate the effects of obesity on breast cancer risk. Our overall results, however, are comparable to those of previous studies, both case-control studies[41] and cohort studies.[7] We have no reason to believe that reporting accuracy should differ by family history. Further, we believe that our face-to-face interviews should have promoted a more honest response from participants, as the interviewer would note observable errors in reporting. It is also possible that exercise history was systematically underreported or overreported by patients or by controls. The first major reference bringing to light the possible relationship between exercise and breast cancer, however, was not published until September, 1994.[11] Most of the study population had already been recruited and interviewed before that time. In addition our systematic method of collecting information on lifetime exercise by creating a record throughout life in conjunction with a calendar of life events should have reduced such biased reporting. This interview approach, known as cognitive interviewing, has proved to be a reliable method for collecting lifetime histories of exercise activity.[42]

Restricting the study to subjects with known age at menopause may have introduced a selection bias into the data. We included subjects with unknown age at menopause, reconstructed the analytic models, and the resulting estimates were similar to the restricted sample.

In summary, our results suggest that exercise and body size measures are modified by family history of breast cancer. Obese women were at a substantially greater risk only if they had a positive family history of breast cancer. Exercise independent of body size seemed to exert a protective effect primarily among women with a negative family history. Women with a positive family history of breast cancer should be especially alert to the importance of maintaining a lean body mass as an important way to lower breast cancer risk after menopause. Exercise activity, by itself, may not be sufficient to reduce breast cancer risk among women with a family history unless accompanied by lean body mass.

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