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Fat or Fit: The Joint Effects of PA, Weight Gain, and Body Size on Breast Cancer Risk

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Abstract

Background—While physical activity reduces breast cancer risk, issues critical to providing clear public health messages remain to be elucidated. These include: the minimum duration and intensity necessary for risk reduction; the optimal time period for occurrence; as well as subgroup effects, particularly with regard to tumor heterogeneity and body size.

Methods—The purpose of this report is to investigate the relationship between recreational physical activity (RPA) and breast cancer risk, in addition to characterizing the joint effects of activity level, weight gain and body size, using a population-based sample of 1504 cases (N=233 in-situ, N=1271 invasive) and 1555 controls (aged 20–98 years) from the Long Island Breast Cancer Study Project.

Results—We observed a non-linear dose response association between breast cancer risk and RPA during the reproductive period and after menopause. Women in the third quartile of activity experienced the greatest benefit with an approximate 30% risk reduction for reproductive (odds ratio [OR]=0.67; 95% confidence interval [CI], 0.48–0.94) and postmenopausal activity (OR=0.70; 95% CI, 0.52–0.95). We observed little to no difference by intensity or hormone receptor status. Joint assessment of RPA, weight gain and body size revealed that women with unfavorable energy balance profiles were at increased breast cancer risk. We observed a significant multiplicative interaction between RPA and adult weight gain (p=0.033).

Conclusions—RPA at any intensity level during the reproductive and postmenopausal years have the greatest benefit for reducing breast cancer risk. Substantial postmenopausal weight gain may eliminate the benefits of regular activity.

Keywords

Breast cancer; physical activity; weight gain; BMI; epidemiology

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Background

Despite the recent downward trend in the rates of breast cancer, with over 200,000 women newly diagnosed with this disease per year[1] it remains an important public health concern. While there has been considerable research in identifying risk factors for breast cancer, a small proportion are amenable to intervention. Physical Activity (PA) appears to play an important role in the reduction of both pre- and postmenopausal breast cancer risk[2–5]. Given that three-quarters of the United States (US) population participates in some PA[6]; it is conceivably one of the most important lifestyle risk factors associated with the breast cancer.

A number of important issues critical to developing public health messages and/or interventions to reduce breast cancer risk, with respect to PA, remain to be elucidated. These include the minimum duration and intensity of PA necessary for risk reduction, as well as the optimal time periods at which activity should occur. A more comprehensive understanding of how this association varies within subgroups may allow us to better target susceptible populations of women for public health messaging and intervention. It may also advance our knowledge of breast cancer etiology. Analyses of subgroups defined by hormone receptor (HR) status may better inform us about the impact of PA in heterogeneous breast tumors. Given the strong association between adiposity and PA[7], simultaneous examination of body weight, PA, and breast cancer risk could help to uncover mechanisms through which PA acts.

The purpose of this report was to: (1) investigate the association between recreational physical activity (RPA), at several points throughout the life-course, and risk of developing breast cancer using data from a large population-based case-control study; (2) explore the association between RPA and HR status to understand if RPA preferentially reduces the risk of HR-positive breast cancers; and (3) characterize the joint effects of activity level and weight gain or body size. We hypothesized that RPA across the life-course was most important for breast cancer risk reduction and that RPA preferentially reduces the risk of HR-positive breast cancers. We also anticipated that women with unfavorable energy balance profiles would be at increased risk of breast malignancy.

Methods

The Long Island Breast Cancer Study Project (LIBCSP) is a population-based study conducted among adult English-speaking female residents of Nassau and Suffolk counties, Long Island, NY. Data used for the analysis reported here include: participants of the case-control study; the case-control interview; and the medical record review. Details of the study methods have been described previously[8]. Institutional Review Board approval was obtained from all participating institutions.

Study Population

Eligible LIBCSP cases were women of all ages (age range 20–98 years) and races newly diagnosed with first primary in-situ or invasive breast cancer between August 1, 1996, and July 31, 1997. Cases were identified through daily or weekly contact to 28 hospitals on Long Island and three large tertiary care hospitals in New York City. Eligible controls were women without a personal history of breast cancer and were frequency matched to the expected age distribution of cases by 5-year age group. Controls were identified through random digit dialing for women under age 65 years and the Health Care Finance Administration rosters for women age 65 years and greater. All data were collected through a two-hour interviewer-administered structured questionnaire conducted by a trained

interviewer in the respondent's home. Interview response among eligible cases and controls were 82.1% (N=1508) and 62.8% (N=1556), respectively.

RPA Assessment

As part of the LIBCSP case-control questionnaire, interviewers asked participants about their involvement in RPA using a modified instrument developed by Bernstein and colleagues[9]. Respondents were asked about all RPA in which they had engaged for at least one hour per week and three months or more in any year over the life-course. Participants who replied never having participated in RPA were classified as having no RPA. Among women who replied ever having participated in RPA, interviewers obtained the activity name, the ages the activity was started and stopped, and the number of hours per week (hrs/wk) and months per year the activity was performed. These data were summed across all activities for each year of a woman's life, providing a lifetime composite score of exercise duration from menarche (left truncated) to reference date. Similarly, for women classified as ever having participated in RPA, metabolic equivalents of energy expenditure (MET) scores were assigned to each reported activity according to a published database[10]. Scores were multiplied by the number of hrs/wk the participant reported engaging in the activity and were summed across all activities. For this ancillary study complete RPA data were obtained for 1,504 cases and 1,555 controls.

Average hrs/wk and average MET hrs/wk of RPA were evaluated in four etiologically relevant time periods based on known windows of breast cancer susceptibility: from menarche to first birth (among parous women), to approximate activity in adolescence and early adulthood; from first birth to menopause (among parous postmenopausal women), to approximate activity during the reproductive years; from menopause to reference date (among postmenopausal women), to approximate activity during the postmenopausal years; and from menarche to reference date, to approximate activity across the lifespan.

Covariate Assessment

In addition to RPA, the case-control questionnaire queried women on demographic characteristics; reproductive, medical and environmental histories; cigarette and alcohol use; use of exogenous hormones; energy intake; and select anthropometric measurements.

Body size assessments included weight, height, and weight change by decade of life. Participants self-reported height to the nearest inch and weight to the nearest pound at age 20 and 1-year prior to reference date. Respondents also reported their weight in each decade of life starting at age 20. Change in weight during two time periods were calculated using methods previously described[11]. Weight change from the 20s to 1-year prior to reference date was used to estimate adulthood weight change, while weight change from the 50s to 1-year prior to reference date estimated postmenopausal weight change. Body mass index (BMI) at age 20 and reference date were calculated for each participant based on the following formula: weight (kg)/height(m)^2.

Among eligible cases clinical data on the characteristics of their breast cancer diagnosis, including HR status, were obtained from medical records.

Statistical Methods

Unconditional logistic regression[12] was used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for associations between breast cancer and RPA. All statistical models were implemented in SAS v.9.1 (Cary, NC).

RPA for the four time periods were evaluated independently as dichotomous variables (using the control median), quartiles, deciles, and as continuous variables. We additionally explored flexible modeling using quadratic functions and linear splines to determine which construction best described the shape of the data. Results produced using quartiles are reported here, as it most adequately captured the dose-response shape of the data employing the fewest number of parameters. To optimize study power for assessment of heterogeneity by HR status and effect measure modification by weight change and BMI, RPA was classified based on the control median (<control median=low RPA; ≥control median=high RPA). Among women who gained weight we classified participants as high (≥control median) or low (<control median) weight gainers for the time periods from age 20 to referent date and from age 50 to referent date. These two groups, along with weight maintainers (+/− 3kg) and weight losers, define our weight change variable. We categorized BMI using the standard World Health Organization (WHO) classifications (<18.5; 18.5–24.9; 25.0–29.9; and ≥30).

We identified potential confounders through the known epidemiology of breast cancer and analysis of causal diagrams[13]. Education (categorical), first degree family history of breast cancer (yes/no), history of benign breast disease (yes/no), income (categorical), lactation history (ever/never), use of oral contraceptives (ever/never), parity (categorical), and smoking history (never, current, former) were considered potential confounders. Covariates resulting in greater than a 10% change in the regression coefficient when added to the model, compared to a model without the covariate, were considered confounders in our final analysis[14]. None of the variables assessed met our criteria. Thus, final multivariable models were adjusted only for the frequency matching factor, 5-year age group.

The main effect of RPA on breast cancer risk was assessed among all women combined as well as within strata of menopausal status. The effect of RPA among postmenopausal women in all four time periods was evaluated by HR status stratifying cases into two groups using information on estrogen receptor (ER) and progesterone receptor (PR) status[15]: women with tumors that showed any hormone responsiveness (ER+/PR+, ER+/PR−, and ER −/PR+) versus none (ER−/PR−).

We examined interactions between RPA, weight change, BMI and postmenopausal breast cancer risk using multiplicative and additive scales. Weight change and BMI were investigated as potential effect measure modifiers based on our a priori study aims. Participants who reported not partaking in RPA over any period during the life-course and had neither gained nor lost weight as an adult were used as a common referent group for the RPA-weight change interactions, while women with no life-course RPA and BMI between 18.5 and 24.99 were used as a common referent group for the RPA-BMI interaction. Departures from the multiplicative null were assessed using the likelihood ratio test, employing $\alpha \leq 0.2$ as a cutoff for statistical significance[16]. Departures from the additive null were evaluated by estimating the interaction contrast ratio (ICR)[17]. Using indicator terms for RPA, weight change, and BMI variables the magnitude of the additive interaction effect was determined by estimating the adjusted ICR based on the following formula: ICR $OR_{11}-OR_{01}-OR_{10}+1$ and its respective confidence interval obtained by ICR±1.96 SE(ICR)[18].

Results

Breast cancer risk among all women was only slightly reduced with ever participation in RPA (OR=0.94; 95% CI, 0.79–1.12) and varied modestly by menopausal status (OR=1.15; 95% CI, 0.80–1.64 for premenopausal women and OR=0.87; 95% CI, 0.71–1.08 for postmenopausal women). While we observed no difference in effects when intensity levels were considered (average MET hours/week) compared to the analysis including duration

alone (data not shown), we did observe some variation by timing of RPA (Table 1). Among premenopausal women neither RPA during adolescence and early adulthood nor RPA over the life-course were associated with breast cancer risk. In contrast, consistent inverse associations between RPA and breast cancer risk were observed among postmenopausal women. Compared to the other time periods, RPA during the reproductive years showed the strongest association. Parous postmenopausal women in the third quartile of activity (10 to 19 hrs/wk) had an age-adjusted OR of 0.67 (95% CI, 0.48–0.94) compared to women who were inactive. The association was also apparent for postmenopausal women in the third quartile of activity performed after menopause (OR: 0.70; 95% CI: 0.52–0.95). Even upon restricting our analyses to parous women creating comparable groups across time periods, we find that the most relevant period for breast cancer risk reduction is during the reproductive period and following menopause (data not shown). Similarly, we found comparable effect estimates for invasive and in-situ cases (data not shown), and thus report findings for total breast cancer.

Among parous postmenopausal women, RPA during the reproductive period was associated with a 25% risk reduction of HR-positive breast cancer (OR=0.75; 95% CI, 0.55–1.03), and a 4% risk reduction among HR-negative cases (OR=0.96; 95% CI, 0.58–1.58) (Table 2). While we observed no statistical differences between HR-positive and HR-negative cases, our exploratory analysis suggests that breast cancer risk reduction from reproductive RPA may apply to women who have the most common types of postmenopausal breast cancer, namely HR-positive tumors. We found no striking results among any of the other three time periods assessed. We also estimated the association between RPA and ER status and found little differences in the two outcome groups. Our data indicate a 15% risk reduction for ER− breast tumors and a 20% risk reduction for ER+ breast tumors among postmenopausal women who were classified as having high reproductive RPA (data not shown).

Our data show that within strata of weight change or BMI women who engage in high activity are at a lower risk of breast cancer than women in the same classification who are inactive (Table 3). High adulthood weight gain was associated with a 28% increased risk of breast cancer among women who engaged in no activity over the life-course (95% CI, 0.68–2.39), while approximately null associations were observed among high gainers reporting high levels of RPA during the same time period (OR=1.02; 95% CI, 0.55–1.87). Similar patterns were observed for high postmenopausal weight gain and obesity although RPA was not shown to mitigate the deleterious effects of high postmenopausal weight gain on breast cancer risk. We found a statistically significant interaction (p=0.033) between lifetime RPA and weight gain from age 20 on the multiplicative scale (Table 3). There was no evidence of interaction on the additive scale.

Discussion

We observed stronger effects for PA among postmenopausal women compared to premenopausal women, which is consistent with previously published data[2–5]. The effects obtained using average MET-hours as a composite measure of intensity and duration were similar to estimates observed for duration alone. Our results did indicate some variations in risk based on timing of RPA occurrence. We found that RPA over the life-course, particularly during the reproductive (among parous women) and postmenopausal years, decreases breast cancer risk. The observed inverse associations are consistent with most other studies that have examined the effect of PA on breast cancer risk reduction[4,5,19,20] where an average 25% risk reduction is reported[5,19].

Results from the current study show that RPA during the reproductive years and after menopause are most critical for risk reduction. Our observations likely reflect the role of PA

in energy balance and obesity mediated mechanisms (e.g. insulin resistance and inflammation) which most commonly manifest after adolescence. We found little evidence of benefit from early-life activity which is consistent with most [21–24], but not all[25,26], investigations. While few studies are able to assess activity across the life-course, those that have a comprehensive lifetime assessment of PA report inverse associations[2,27]. Using a similar PA assessment to the current study, Bernstein and colleagues report a 17% risk reduction among women in the highest quartile of lifetime activity compared inactive women[27]. We also found a 17% risk reduction for lifetime RPA among the most active women despite our wide age distribution (age 20–98 vs. age 35–64). Given the noticeable difference in age distribution for this study, we re-assed our main effects restricted to women age <80, <70, and <60 years, respectively. We found no difference between these restricted analyses and the analyses among women of all ages (data not shown).

Contrary to a recent review which reports an inverse dose-response association between PA and breast cancer risk[5], the observed effect for RPA did not decrease in a dose-response manner. A lack of linear dose-response could be interpreted as weak evidence of an association between RPA and breast cancer risk. However, it is possible that the RPA breast cancer association may follow a J- or U-shape. In the LIBCSP, a substantial proportion of women reported high levels of RPA permitting us to consider a wide range of effects. Studies indicate that sustained PA is a strong inducer of lipid peroxidation and reactive oxygen species[28,29]. These changes may cause DNA damage, mutations in proto-oncogenes or tumor-suppressor genes and, if unrepaired, transformation of normal epithelium to a malignant phenotype[30,31]. Studies also show that vigorous physical exercise may depress immune function[32]. Inconsistencies in dose-response may therefore reflect the underlying distribution of RPA among study participants. For example, the median lifetime RPA in the Women's Contraceptive and Reproductive Experiences study was 1.2 hrs/week[27], while the median lifetime RPA was 6.35 hrs/week in the current study. Our results, in combination with animal and clinical data, suggest that sustained involvement in vigorous activity may mitigate the known protective effect of RPA resulting in a J- or U-shaped association.

Although our results do not show statistically significant associations among HR-positive or HR-negative cases, they do suggest that RPA during the reproductive period may preferentially decrease HR-positive tumors. This further supports the hypothesis that breast cancer is a heterogeneous disease with varying etiologic pathways[33]. When we assessed ER-negative cases compared to ER-positive cases the patterns of association were not markedly different between groups (OR=0.80 and 0.85, respectively), suggesting that the role of PA in risk reduction is not entirely mediated through an estrogen pathway. It should be noted that in these analyses the cell sizes were particularly small for ER−/PR− cases in comparison with any positive cases. Our findings are comparable to other reports that find no difference in the PA-breast cancer association by hormone receptor status[27,34,35], but in contrast to some studies which report greater decreases among ER- cases compared to ER+ cases[35,36], and still others which show stronger associations for ER+ tumors[37,38].

In this large case-control study we found that breast cancer risk was generally the greatest among women jointly classified as having high levels of adiposity and little RPA. While the results were consistent with our hypothesis, we found only one multiplicative interaction and no evidence of additive interaction among our indicators of energy balance. It is noteworthy that postmenopausal RPA reduced the adverse effects of obesity on breast cancer risk to approximately null, but did not completely obliterate the effect of postmenopausal weight gain. These observations likely reflect differences in the effect of weight maintenance vs. weight gain[39] with the latter being potentially more deleterious during the postmenopausal years[11]. The timing of weight gain may therefore be an important factor in understanding the weight-PA interaction among postmenopausal populations. While stratification would

help us better uncover these associations, even with a study sample of 3000 women we did not have adequate statistical power to evaluate the three-way joint effects of weight gain, BMI and RPA. Few studies have examined modification by weight change[40–44]. In the only other study[42] to assess the joint effects of weight gain and PA using the common referent analysis, investigators also reported that high PA did not eliminate the excess breast cancer risk caused by weight gain.

Studies of PA and breast cancer risk have mixed results on the modifying effects of BMI. Several investigations have found risk reductions only among physically active lean women[43–48], while others report risk reductions in all BMI categories[42,49]. A 2008 review of 16 studies estimated that risk reductions were approximately 25% among women with BMI between 22 and 25 kg/m2 and 20% among women with BMI ≥25 kg/m2. There were near null effects of PA on breast cancer risk among women with BMI ≥30 kg/m2, although few studies reported effects in this stratum[5]. Our results are consistent with this review.

The strengths of our study are numerous and include its population-based design and large sample size which increased our power to detect small associations, assess subgroup analyses, and evaluate joint effects of weight indicators and RPA. Our RPA assessment provided a wide range of activities that contribute to energy expenditure in this population of women. Multiple time periods throughout the lifespan were evaluated as well as several parameters of RPA. While in this analysis we were unable to assess all potential sources of PA, a comprehensive 2008 review of physical activity parameters and breast cancer risk showed that the greatest risk reductions were for RPA (20% risk reduction). Activity related to occupation, transportation and living each resulted in ~14% risk reduction[5]. Few studies have considered PA from all sources. Given the high socioeconomic status and of Long Island women[8] we expected little variation by alternative sources of activity and anticipate that any additional variation would result in a more pronounced risk reduction. Although our RPA measurement has not been validated, this instrument was useful in revealing important relationships between exercise and breast cancer risk in other epidemiologic studies[9,50].

Despite the large overall sample size a limitation of this study was its relatively homogenous population. Study participants were on average more affluent and educated than the US population. Results are therefore not readily applicable to all women. Our study population included few women who were nulliparous[8]. We were therefore unable to perform a stratified analysis by nulliparity when assessing the effect of timing on breast cancer risk. Errors in reporting or differential reporting by cases and controls have the potential to bias the study results. A spurious inverse association could have occurred if PA was systematically underreported by cases or over reported by controls. While regular PA, like other healthy behaviors, may result in some social desirability, we suspect that these biases would persist in both case and control groups resulting in non-differential misclassification of RPA. Given the exposure variable was not simply dichotomous however, the direction of such a bias would be unpredictable[51]. To reduce the probability of recall bias and misclassification, Long Island investigators used a comprehensive questionnaire to obtain detailed information on most study variables enhancing our ability to assess RPA and control for confounding by important breast cancer risk factors.

Conclusion

In this large population-based study that included a life-course assessment of RPA and body size, we found that frequent episodes of RPA (10 to 19 hrs/wk) at any intensity level during the reproductive and postmenopausal years may have the greatest benefit for reducing the risk of breast cancer. Our data indicate, however, that substantive postmenopausal weight gain may eliminate the benefits of regular RPA. Collectively, these results suggest that

women with can still reduce their breast cancer risk later in life by maintaining their weight and engaging in moderate amounts of activity. Future investigations should include populations with wide distributions of PA to confirm the non-linear dose-response found in this study.

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TABLE 1

Age Adjusted Odds Ratios and 95% Confidence Intervals for the Association between Recreational Physical Activity at four Time Periods and Breast Cancer Risk in the Long Island Breast Cancer Study Project (1996–1997).

Time period and quartile of RPA (average hrs/wk)	*Pre and Postmenopausal women N=1504 Cases; N=1555 Controls*			*Premenopausal women only N=472 Cases; N=503 Controls*			*Postmenopausal women only N=1003 Cases; N=989 Controls*		
	Ca/Co	**OR**	**95% CI**	**Ca/Co**	**OR**	**95% CI**	**Ca/Co**	**OR**	**95% CI**
Participation in RPA									
Never	334/318	1.00	Reference	69/79	1.00	Reference	255/224	1.00	Reference
Ever	1170/1237	0.94	(0.79–1.12)	403/424	1.15	(0.80–1.64)	748/765	0.87	(0.71–1.08)
Menarche to first birth (among parous women)									
None	449/482	1.00	Reference	111/122	1.00	Reference	331/343	1.00	Reference
Q1 (≤ 1.97)	211/207	1.14	(0.90–1.44)	81/86	1.13	(0.75–1.69)	124/113	1.14	(0.85–1.56)
Q2 (1.98–5.23)	215/206	1.15	(0.92–1.48)	71/76	1.04	(0.68–1.59)	140/121	1.22	(0.91–1.63)
Q3 (5.24–12.00)	188/209	1.00	(0.79–1.27)	75/64	1.30	(0.85–2.00)	112/133	0.90	(0.67–1.21)
Q4 (≥ 12.01)	176/203	0.96	(0.75–1.22)	50/61	0.93	(0.58–1.47)	120/133	0.96	(0.72–1.29)
First birth to menopause (among parous women)									
None							265/230	1.00	Reference
Q1 (≤ 3.84)							113/125	0.82	(0.60–1.13)
Q2 (3.85–10.00)		*N/A*			*N/A*		157/132	1.06	(0.79–1.43)
Q3 (10.01–18.95)							90/116	0.67	(0.48–0.94)
Q4 (≥ 18.96)							121/124	0.86	(0.63–1.17)
Menopause to reference date									
None							254/223	1.00	Reference
Q1 (≤ 3.65)							155/145	0.90	(0.67–1.21)
Q2 (3.66–9.23)		*N/A*			*N/A*		174/145	1.07	(0.80–1.43)
Q3 (9.24–16.98)							118/145	0.70	(0.52–0.95)
Q4 (≥ 16.99)							144/145	0.84	(0.63–1.13)
Menarche to reference date									
None	341/333	1.00	Reference	70/89	1.00	Reference	261/229	1.00	Reference
Q1 (≤ 2.14)	281/289	1.00	(0.79–1.25)	113/105	1.45	(0.95–2.20)	166/173	0.85	(0.65–1.13)
Q2 (2.15–6.35)	288/283	1.06	(0.85–1.33)	106/118	1.24	(0.82–1.88)	176/155	1.03	(0.77–1.36)
Q3 (6.36–13.45)	261/286	0.93	(0.74–1.17)	93/94	1.30	(0.84–2.01)	164/182	0.81	(0.61–1.07)

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Time period and quartile of RPA (average hrs/wk)	*Pre and Postmenopausal women N=1504 Cases; N=1555 Controls*			*Premenopausal women only N=472 Cases; N=503 Controls*			*Postmenopausal women only N=1003 Cases; N=989 Controls*		
	Ca/Co	**OR**	**95% CI**	**Ca/Co**	**OR**	**95% CI**	**Ca/Co**	**OR**	**95% CI**
Q4 (≥ 13.46)	263/285	0.92	(0.74–1.16)	79/79	1.32	(0.84–2.07)	177/191	0.83	(0.63–1.09)

Ca, cases; Co, controls; OR, odds ratio; 95% CI, 95% confidence interval; Q, quartile of recreational physical activity

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TABLE 2

Age Adjusted Odds Ratios and 95% Confidence Intervals for the Association between Recreational Physical Activity Hormone Receptor Status among Postmenopausal Women in the Long Island Breast Cancer Study Project (1996–1997).

Time period of RPA	HR negative cases (N=132) vs. All Controls (N=990)			HR positive cases (N=538) vs. All Controls (N=990)		
	Ca/Co	OR	95% CI	Ca/Co	OR	95% CI
Menarche to first birth (among parous women)						
None	44/343	1.00	Reference	177/343	1.00	Reference
Low RPA (≤ 5.23 hrs/wk)	36/234	1.19	(0.73, 1.93)	136/234	1.18	(0.89, 1.57)
High RPA (> 5.23 hrs/wk)	33/266	0.98	(0.60, 1.60)	128/266	1.01	(0.76, 1.34)
First birth to menopause (among parous women)						
None	37/230	1.00	Reference	143/230	1.00	Reference
Low RPA (≤ 10.00 hrs/wk)	36/257	0.90	(0.54–1.49)	146/257	0.98	(0.72–1.32)
High RPA (> 10.00 hrs/wk)	36/240	0.96	(0.58–1.58)	107/240	0.75	(0.55–1.03)
Menopause to reference date						
None	34/223	1.00	Reference	137/223	1.00	Reference
Low RPA (≤ 9.23 hrs/wk)	41/290	0.92	(0.56–1.52)	171/290	0.94	(0.70–1.26)
High RPA (> 9.23 hrs/wk)	40/290	0.90	(0.55–1.49)	146/290	0.80	(0.59–1.08)
Menarche to reference date						
None	30/229	1.00	Reference	14/229	1.00	Reference
Low RPA (≤ 6.35 hrs/wk)	45/328	1.08	(0.65, 1.79)	180/328	0.93	(0.70, 1.24)
High RPA (> 6.35 hrs/wk)	48/373	1.05	(0.64, 1.73)	190/373	0.87	(0.66, 1.15)

Ca, cases; Co, controls; OR, odds ratio; 95% CI, 95% confidence interval; HR Negative, ER− and PR−; HR Positive, any ER+ or PR+

TABLE 3

Age Adjusted Odds Ratios and 95% Confidence Intervals for the Joint Effect of Body Size and Recreational Physical Activity among Postmenopausal Women on Breast Cancer Risk in the Long Island Breast Cancer Study Project (1996–1997)

	Recreational Physical Activity (average hours per week)										
Body Size Measurement	**Ca/Co**	***No RPA***		**Ca/Co**	***Low RPA***		***ICR (95% CI)***	**Ca/Co**	***High (RPA)***		***ICR (95% CI)***
		OR	**95% CI**		**OR**	**95% CI**			**OR**	**95% CI**	
Weight gain since age 20 (kg) in relation to lifetime RPA (Postmenopausal women: Total Ca/Co = 927/917)											
Maintain	26/24	1.00	reference	30/44	0.70	(0.33,1.46)		37/41	0.97	(0.47,1.99)	
Lose	13/13	1.05	(0.40,2.76)	12/25	0.48	(0.20,1.18)	*−0.27 (−2.08,1.54)*	7/21	0.31	(0.11,0.88)	*−0.71 (−2.50,1.09)*
Low gain	90/78	1.19	(0.62,2.27)	144/150	1.03	(0.56,1.90)	*0.14 (−1.75,2.03)*	132/138	0.99	(0.54,1.84)	*−0.16 (−2.21,1.88)*
High gain	126/106	1.28	(0.68,2.39)	151/109	1.48	(0.79,2.75)	*0.50 (−1.72,2.72)*	159/168	1.02	(0.55,1.87)	*−0.23 (−2.31,1.86)*
p for multiplicative interaction										0.033	
Weight gain since menopause (kg) in relation to postmenopausal RPA (Postmenopausal women: Total Ca/Co = 795/743)											
Maintain	39/44	1.00	reference	59/72	0.94	(0.54,1.63)		41/54	0.85	(0.47,1.54)	
Lose	48/37	1.39	(0.75,2.57)	50/51	1.02	(0.57,1.83)	*−0.31 (−2.17,1.56)*	33/49	0.66	(0.35,1.24)	*−0.58 (−2.21,1.06)*
Low gain	64/55	1.27	(0.72,2.24)	85/74	1.23	(0.72,2.11)	*0.03 (−1.81,1.87)*	75/94	0.84	(0.49,1.44)	*−0.27 (−1.87,1.33)*
High gain	93/61	1.57	(0.91,2.72)	112/78	1.48	(0.87,2.52)	*−0.02 (−2.12,2.07)*	96/74	1.35	(0.79,2.32)	*−0.07 (−2.09,1.96)*
p for multiplicative interaction										0.646	
BMI at reference date (kg/m2) in relation to postmenopausal RPA (Postmenopausal women: Total Ca/Co = 832/790)											
< 18.5	4/6	0.55	(0.15,2.07)	3/4	0.70	(0.15,3.32)		3/7	0.34	(0.08,1.40)	
18.5–24.99	91/83	1.00	reference	127/140	0.84	(0.57,1.23)	*0.31 (−1.54,2.17)*	93/115	0.73	(0.48,1.09)	*0.07 (−0.94,1.07)*
25.0–29.99	75/66	1.02	(0.65,1.60)	121/87	1.26	(0.84,1.89)	*0.40 (−0.74,1.53)*	94/98	0.85	(0.56,1.29)	*0.10 (−0.86,1.06)*
≥ 30.0	79/62	1.17	(0.74,1.83)	73/57	1.17	(0.74,1.86)	*0.17 (−0.96,1.30)*	69/65	0.99	(0.62,1.55)	*0.09 (−1.10,1.29)*
p for multiplicative interaction										0.454	

Ca, cases; Co, controls; OR, odds ratio; 95% CI, 95% confidence interval; RPA, recreational physical activity; ICR, interaction contrast ratio

Weight loss: < −3kg; Weight Maintenance: +/− 3kg; Weight gain: > +3kg