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Physical Activity and Risk of Male Breast Cancer

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Abstract

The association between leisure-time physical activity (LTPA) and male breast cancer risk (MBC) is unclear. In the MBC pooling project, with 449 cases and 13,855 matched controls, we used logistic regression with study stratification to generate adjusted odds ratios (OR) and 95% confidence intervals (CI) for LTPA tertiles and MBC risk. Compared with low LTPA, medium and high LTPA were not associated with MBC risk (OR=1.01, 95% CI 0.79–1.29; 0.90, 0.69–1.18, respectively). In joint-effects analyses, compared with the referent of high body mass index (BMI) (≥25 kg/m^2)/low LTPA, neither medium nor high PA were associated with risk among high BMI men, but normal BMI men (<25 kg/m^2) with low or medium LTPA were at a non-significant ~16% reduced risk and those with high LTPA were at a 27% reduced risk (OR=0.73, 95% CI 0.50–1.07). Physical activity alone may not confer protection against MBC risk.

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Keywords

Male breast cancer; epidemiology; physical activity; pooled analysis

Introduction

Male breast cancer (MBC) is a rare disease, with a lifetime risk of 1 in 1,000. Due in part to the rarity of this cancer, relatively few studies have examined lifestyle-related etiologic factors. Leisure time physical activity (LTPA) has been consistently associated with a lower risk of postmenopausal female breast cancer(1, 2), but associations with MBC are unclear. Previous studies of physical activity and MBC risk suggest inverse—but not statistically significant—associations(3–6), yet were based on small case numbers and study characteristics or designs (proxy respondents(6), case-control(4, 5)) that may capture physical activity differently than a prospective design with self-reported data. In this analysis, with more cases and predominately prospectively collected data, we hypothesized that moderate to vigorous-intensity LTPA would be associated with a lower MBC risk.

Materials and Methods

Methods for the Male Breast Cancer Pooling Project (MBCPP) have been previously published(7). In short, the MBCPP identified all case-control or cohort studies with ≥10 cases using literature searches of PubMed, citations within published manuscripts, and advertisements at the National Cancer Institute Cohort Consortium meetings(7). Of the 21 studies identified for inclusion in the MBCPP, 10 had collected baseline information on LTPA (nine prospective nested case-control studies(8–16) and one retrospective case-control study(4)). The 2 cohort studies and 10 case-control studies that were not included in our analysis did not ask detailed information on LTPA and thus were not eligible for this analysis. Characteristics of included studies are presented in Supplementary Table S1. Cases were defined by the International Classification of Diseases, 10th Edition code C50 from cancer registries, medical record, or self-report. All studies contributed de-identified data following approved data sharing agreements, as well as National Cancer Institute and study center institutional review board clearances. Participants gave informed consent by nature of study participation.

LTPA was harmonized across studies into categories of low, medium and high. Studies with a single LTPA question on frequency of activity (AARP, JANUS, PHS, PLCO, Kaiser Permanente) ranged from four to six response levels. For example, in the PHS, the frequency question was “How often do you exercise vigorously enough to work up a sweat?”, with six categorical choices ranging from daily to rarely/never. In these studies we collapsed the categories to create a relatively even distribution for low, medium and high. For studies with line items for more than one type of activity (Canada, CPS II-NC, EPIC, HPFS, MEC), we assigned metabolic equivalent hours per week, using intensity values previously assigned by individual studies and by referencing the updated Ainsworth Compendium of Physical Activities (17). Example activities from HPFS included separate line items with 10 categorical responses ranging from none to 11+ h/wk for walking

outdoors, jogging, running, bicycling, lap swimming, tennis, squash, or calisthenics/rowing. We then divided the study-specific distributions into categories of low (<33rd percentile), medium (33–<66th percentile), and high (≥66th percentile) LTPA.

We used unconditional logistic regression with stratification by study to compute odds ratios (OR) and 95% confidence intervals (95% CI). We first created models adjusted for age, and then additionally adjusted for race, education, marital status, diabetes history, alcohol, smoking status, and body mass index (BMI). We created missing categories for race, education, marital status, diabetes, and alcohol, as these covariates were missing for ≤5% of study subjects, and for alcohol, for which 13% were missing. Sensitivity analyses excluding observations with missing data yielded unaltered results. To assess influence by individual studies, we also performed analyses excluding one study at a time.

Because BMI was previously associated with MBC risk in this population (7), and because joint effects of BMI and physical activity have been observed for female breast cancer risk, we created six categories to look at joint effects: high BMI (≥25 kg/m^2) with 1) low (referent), 2) medium or 3) high activity levels, and normal BMI (<25 kg/m^2) with 4) low, 5) medium or 6) high activity levels. We also stratified analyses by age, BMI, diabetes, smoking and family history of breast cancer and assessed interactions using the Wald test. All analyses were performed using SAS V9.3 (SAS Institute Inc, Cary, NC). P-values <0.05 were considered significant.

Results

This pooled analysis of 10 studies included 449 cases and 13,855 controls. More active men were more likely to be non-Hispanic white, college graduates, have a lower BMI, and were less likely to be current smokers or report diabetes (Table 1).

Compared with men reporting low LTPA, men reporting medium and high LTPA levels did not have a lower MBC risk after adjustment for other risk factors (OR=1.01, 95% CI 0.79–1.29; 0.90, 0.69–1.18, respectively) (Table 2). Results were similar after excluding one study at a time to test undue influence by an individual study (Supplementary Table S2).

In joint effects analyses of BMI and LTPA we found that among high BMI men (≥25 kg/m^2) neither medium nor high LTPA were associated with risk (OR=1.01, 95% CI 0.76–1.34; 0.90, 0.66–1.24, respectively) compared with the referent group of low LTPA/high BMI; However, non-significant ~16% lower risks were observed among normal BMI men (<25 kg/m^2) who reported either low or medium LTPA (OR=0.83, 95% CI 0.58–1.19; 0.84, 0.59–1.18, respectively), and a non-significant 27% lower risk was observed among men who had a normal BMI/ high LTPA (OR=0.73, 95% CI 0.50–1.07) (Table 2).

Stratified analyses did not suggest statistically significant interactions by median age, BMI, diabetes, or family history of breast cancer (all $p_{interaction}$-values ≥0.05; Supplementary Table S3). There was a stronger inverse association between LTPA and MBC among current smokers (OR=0.25, 95% CI 0.07–0.85) than among never or former smokers, with the p-interaction showing borderline significance (p=0.05).

Discussion

Previous studies of LTPA and female breast cancer risk have suggested stronger risk reductions of about 25% among postmenopausal normal weight women compared to no association for obese women(2), which is similar to the magnitude of association we found among active men with a normal BMI.

Published MBC studies have shown non-significant inverse associations with LTPA, but were based on limited numbers (range=81–178)(3–6) and faced challenges of collecting PA data from proxy respondents of deceased men(6), and retrospective (case-control designs), which may introduce recall bias(4, 5). Reasons for a possible interaction of LTPA with BMI remain unknown, but may reflect the cumulative effect of reduced estrogen exposure for lean active men, supported by other findings from the MBCPP of elevated risks being associated with both high BMI(7) and higher estradiol(18).

Strengths of this study include the relatively large sample size, prospective data collection in nine of the ten studies, and use of studies with sufficiently detailed information on LTPA. Limitations of this analysis include the inability to stratify by genetic MBC risk factors such as Klinefelter's syndrome or BRCA status, as this information was not available. We also had LTPA and BMI data only from baseline, which does not account for changes in these factors over time. We captured only leisure-time activity in this study, and were unable to examine occupational activity or sedentary time, each of which may affect risk. In summary, our findings suggest that physical activity alone may not be protective for MBC risk.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Baseline characteristics of the pooled study populations of male breast cancer cases (n=449) and controls (n=13,855)

	Physical activity tertile[a]		
Characteristic	**Low**	**Medium**	**High**
Cases/controls	157/3884	177/5757	115/4214
Age at entry (years), mean (SD)[b, c]	61.0 (7.9)	61.7 (7.6)	62.1 (7.7)
Race, n (%) white[b]	3499 (86.8)	5293 (89.9)	3882 (90.2)
Married, n (%)	3316 (85.3)	5064 (87.3)	3625 (87.5)
Body mass index (kg/m^2), mean (SD)	27.3 (4.4)	26.7 (3.8)	26.0 (3.3)
Smoking status, n (%)			
Never	1269 (32.3)	2006 (34.9)	1479 (35.2)
Former	1990 (50.7)	3131 (54.4)	2352 (56.0)
Current	668 (17.0)	615 (10.7)	372 (8.9)
Diabetes, n (%)			
No	3333 (91.0)	5280 (91.7)	3832 (93.0)
Yes	328 (8.9)	480 (8.3)	288 (7.0)
Alcohol (grams/day), mean (SD)	17.3 (40.6)	15.4 (33.7)	15.7 (30.3)
Educational level, n (%)			
Less than high school	683 (17.3)	457 (7.9)	389 (9.2)
High school graduate	625 (15.8)	803 (13.8)	650 (15.3)
Some college/vocational school	914 (23.1)	1485 (25.5)	985 (23.2)
College graduate	1728 (43.8)	3069 (52.8)	2229 (52.4)

[a] Physical activity tertiles were created from study specific distributions and then pooled.

[b] Cohort control subjects were incidence-density matched to cases on sex, race, study center, date of birth, date of entry, and exit date.

[c] Case-control subjects were frequency matched on age, and were sampled from provincial health insurance plans in Canada (coverage of >95% of Canadians).

Table 2

Odds ratios and 95% confidence intervals for physical activity and risk of male breast cancer (n=449 cases/ 13855 controls)

Physical Activity level	Low	Medium	High	p-trend
N (case/control)	157/3884	177/5757	115/4214	
Model 1[a]	1.00	1.04 (0.81–1.32)	0.92 (0.70–1.19)	0.515
Model 2[b]	1.00	1.00 (0.79–1.28)	0.88 (0.68–1.15)	0.362
Model 3[c]	1.00	1.01 (0.79–1.29)	0.90 (0.69–1.18)	0.443
Joint effects[b]				
High BMI (≥25 kg/m^2)	1.00	1.01 (0.79–1.34)	0.90 (0.66–1.24)	
Normal BMI (<25 kg/m^2)	0.83 (0.58–1.19)	0.84 (0.59–1.18)	0.73 (0.50–1.07)	

[a] Model 1 included stratification by cohort and was adjusted for age.

[b] Model 2 was additionally adjusted for race (white, black, other), educational level (high school or less, some college, completed college), marital status (married, not married), history of diabetes (yes, no), alcohol consumption (none, 1–2 drinks/day, >2 drinks/day), and smoking status (never, former, current).

[c] Model 3 was additionally adjusted for body mass index (<18.5, 18.5–<25, 25–<30, 30+ kg/m^2).