Lifetime physical activity and risk of breast cancer in pre-and post-menopausal women

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Abstract

Purpose: To investigate the association between different types of physical activity (PA) and breast cancer. **Methods:** A case-control study of breast cancer was conducted in Western Australia from 2009-2011, in which 1202 women with breast cancer and 1785 frequency age-matched breast cancer-free control women were recruited. A self-administered questionnaire was used to collect information about lifetime and age-period recreational, household, occupational and transport physical activities. Detailed questions about demographic characteristics, and relevant reproductive, medical and lifestyle factors were also included. Logistic regression and restrictive cubic spline analyses were applied to investigate the association and dose-response relationship between PA and breast cancer risk. Sub-group analysis was performed regarding menopausal status. **Results:** We found non-linear dose-response associations between PA and risk of breast cancer. Overall, 95-130 MET-hours/week of total lifetime PA was associated with the lowest breast cancer risk. The effects were stronger among post-menopausal women. We also found medium amounts of recreational PA (up to 21 MET-hours/week) were associated with lower breast cancer risk among post-menopausal women. Further analysis on the intensity of recreational PA demonstrated different dose-response associations between moderate- and vigorous-intensity recreational PA and breast cancer risk. **Conclusions:** We found that physical activity was associated with a reduced risk of breast cancer among post-menopausal women, but not in a linear fashion. Recreational PA of different intensities may have different dose-response associations with risk of breast cancer.

Key words: Physical activity; Recreational physical activity; breast cancer; dose-response association

Introduction

Breast cancer is the most commonly diagnosed invasive cancer in Australian women. It was also the sixth leading cause of burden of disease for females in 2012.[1] The health expenditure on breast cancer was estimated to be $331 million in 2004-2005, accounting for 24% of all cancer expenditure for Australian women that year.[1] Most identified risk factors for breast cancer are non-modifiable in nature including age, height, family history, hormonal factors and child-bearing histories.[1] Nevertheless, some modifiable lifestyle-related risk factors for breast cancer have been identified, including physical activity (PA).[1] A review identified over 73 epidemiologic studies (including cohort and case-control studies) investigating the associations or dose-response relationships of PA and the risk of breast cancer worldwide.[2] Although results of these studies were divergent, a slight majority (51% of all studies) concluded that increasing PA significantly reduced the risk of breast cancer. Case-control studies, with an average risk reduction of 30%, generally yielded stronger effects than cohort studies for which the average risk reduction was 20%.[2] Similarly, a meta-analysis of 31 prospective cohort studies yielded an overall 23% risk reduction in breast cancer related to PA.[3]

To establish a causal relationship between PA and reduced risk of breast cancer, potential biological mechanisms have been investigated and verified. It has been argued that PA decreases lifetime exposure to oestrogen by delaying menarche, reducing the number of ovulatory cycles and ovarian oestrogen production. [4] Higher levels of other sex hormones including testosterone and androstenedione have also been associated with an increased risk of breast cancer, especially among post-menopausal women; and PA might lower testosterone levels. [5] Increasing epidemiological evidence indicates that adiposity and change of body composition (waist circumference/abdominal fat) is associated with risk of breast cancer, especially among post-menopausal women. [6-8] Other possible biological pathways related to PA and risk of breast cancer have also been investigated including insulin-related factors, adipokines and inflammatory cytokines. However, limited epidemiological evidence has been found to verify these pathways.[2]

Many studies have investigated the dose-response relationship between PA and risk of BC. While some studies yielded linear association, several studies suggest a ceiling effect of lifetime PA in reducing risk of breast cancer, in which study participants with the highest level of PA were not the group at the lowest risk of breast cancer.[9-14] Types of physical activity (e.g. aerobic activity, weight lifting) may vary with regard to different domains of physical activity (e.g. recreational, occupational or household PA), therefore physical activity in different domains may have distinctive effects on breast cancer risk.[9] A meta-analysis of prospective cohort studies yielded 10% to 16% reduction in breast cancer risks with different domains of PA including recreational, occupational and household PA.[3] However, the definition and content of domains of PA varied in these studies. [10-13, 15-21]

Besides domains of PA, the intensity of PA may also influence the association between physical activity and breast cancer risk. A review concluded that moderate and vigorous intensity PA are associated with breast cancer risk reductions in the order of 15% and 18% respectively,[2] while there is some evidence that light-intensity physical activity may be inversely associated with the risk of breast cancer.[22] Similarly, the meta-analysis of prospective cohort studies reported 5% and 15% risk reduction related to moderate and vigorous PA respectively.[3] Even though the evidence seems to suggest stronger effects of vigorous-intensity PA on breast cancer risk reduction, current recommendations for recreational physical activities tend to make the assumption that moderate- and vigorous-intensity PA are related in terms of energy expenditure, with double the amount of moderate-intensity equivalent to vigorous-intensity PA.[23, 24]

The aim of our study was to investigate the relationships between risk of invasive breast cancer and physical activity including recreational, occupational, transport and household PA and PA of different intensity. As some breast cancer risk factors may vary for pre- and post-menopausal women (such as obesity,[2] and since most evidence suggests stronger associations of physical activities and risk of breast cancer in post-menopausal women,[2] subgroup analyses were performed based on menopausal status. Additionally, we investigated the dose-response associations of moderate- and vigorous-intensity recreational PA with risk of breast cancer.

Methods

Exposure to PA was collected as part of the case-control study, Breast Cancer Employment and Environment Study (BCEES). The details of patients' eligibility and recruitment procedures for this case-control study are described elsewhere.[25] In brief, women aged between 18 and 80 years with primary invasive breast cancer diagnosed between May 2009 and January 2011 were identified from the Western Australia (WA) Cancer Registry. Frequency age-matched control participants, who had not been diagnosed with invasive breast cancer, were randomly selected from the WA electoral roll during the same time period.

Informed consent was obtained for all study participants. The study was approved by the Human Research Ethics Committees of The University of WA and the WA Department of Health.

Data collection

All participants were sent an invitation letter, consent forms and a study questionnaire. Questions regarding demographic characteristics (age, education level, socio-economic status, remoteness of residence), reproductive history (pregnancy and breastfeeding history), family history of breast cancer, lifestyles (alcohol consumption and smoking status), Body Mass Index (BMI) and reproductive history (menopausal status, age at menarche, oral contraceptive use, Hormone Replacement Therapy use (HRT)) were included in the questionnaire.[25]

Participants were asked to provide information on any job or occupations that they had held for at least 6 months in their lifetime. Questions included: age started, duration in years, job title, main duties, employer, industry, country of employment, hours per week, weeks per year worked and their self-rated intensity of activity (sedentary occupation, standing occupation, manual work and heavy manual work). This occupational activity question has been shown to have acceptable reliability and validity when measuring current activity.[26] Additionally, self-rated occupational activity and job-title based occupational activity have been shown to have very high agreement (kappa = 0.73) in this study population.[27]

A modified version of the Chasan-Taber Physical Activity Questionnaire (CT-PAQ) was used to assess recreational (walking, swimming, dancing, tennis, aerobics, netball and squash, and up to three other activities) and household (gardening and household chores) PA, with new questions added to assess transport-related PA (cycling and walking to/from work).[28] Both the CT-PAQ and the new transport-related physical activity questions have been shown to have acceptable test-retest reliability.[28, 29] Recreational, household and transport-related PAs were reported in three different age periods: 15-24 years, 25-39 years and 40 years above. Questions about age when the PA started and the number of years, months per year and hours per week undertaking each activity were included to quantify each PA undertaken.

Exposure assessment

Physical activities

All PAs were assigned a metabolic equivalent (MET) value, derived from the Compendium of Physical Activities.[30] One MET is defined as the ratio of the metabolic rate for a specific activity compared to the resting metabolic rate. [30] MET-values were assigned to all measured PA in recreational, household, occupational and transport domains. For example, walking for exercise was assigned a MET-value of 4.3; swimming of 6; gardening of 3.8 and cycling to and from work of 7.5. MET-value of 1.5, 2.3, 3.5 and 6 were assigned to the four categories of occupational activities of sedentary, standing, manual and heavy manual occupations respectively. The intensity of each PA was classified as light, moderate or vigorous based on the MET-value assigned to it. Any PA with assigned MET-value between 1.6 and 3 was labelled light PA; the ones with assigned MET-value between 3 and 6 were classified as moderate PA; any PA with assigned MET-value 6 and above was classified as vigorous PA. MET-hours/week of each activity was calculated by multiplying the MET-value by its frequency and duration. For each age-period and over the lifetime, and for domain-specific and all physical activity (i.e., the four domains combined), we then calculated mean MET-hours per week in light-intensity PA, moderate-intensity PA, vigorous-intensity PA and total PA (i.e., light, moderate and vigorous PAs combined).

Menopausal status

Participants were classified as post-menopausal if they self-reported being post-menopausal; or were aged over 51 years and above and had one of the following self-reported conditions: use of HRT with regular periods; do not have regular period because of history of hysterectomy or oophorectomy; do not have regular period because of cancer treatment; or irregular periods (due to stress, endometriosis or relevant treatment; polycystic ovary; tubal ligation; or other endocrine disorders, etc.) We conservatively assumed that if women were missing information on whether they had regular periods and were over age 51 that they were postmenopausal.

Potential confounding factors

Potential confounding factors collected in the study questionnaire included: age, socio-economic status (derived from residential postcode and the index of relative socioeconomic advantage and disadvantage for area [31], index of remoteness of residence (ARIA)[32], education attainment, family history of breast cancer, age at menarche, age at first pregnancy, breastfeeding history, oral-contraceptive use in the past 5 years, self-reported hormone replacement therapy use, alcohol consumption, smoking status and current BMI.

Family history of breast cancer was assessed in line with the Australian clinical guidelines:[33] "High risk" was assigned if the participant reported a first-degree female relative diagnosed with breast cancer before the age of 50, or two or more first-degree or second-degree female relatives with breast cancer on the same side of the family; "some family history" was assigned to respondents who reported any first-degree or second-degree female relative diagnosed with breast cancer at any stage; and all others were assigned "no family history".

Data analysis

Data management

Those jobs with missing occupational activity intensity were assigned either the level of a similar job the same participant had held (based on their self-reported job titles and main job duties), or a physical demands strength rating (based on job-title and duties) from the Dictionary of Occupational Titles if the participant had not reported the activity level of a similar job.[34] Missing information on hours per week or weeks per year for a job was assigned the median values of the existing/remaining records (of the same variable) from each individual. The missing duration of a job was calculated by subtracting the age started at the current job from the age started at the following job.

Hours per week were truncated at 14 hours per week for each individual recreational and transport-related activity, and household chores were truncated at 40 hours per week. If a participant was missing data for months per year and/or hours per week for an activity, and they had performed the same activity in a previous or subsequent age-period, the value(s) from that age-period were used. If they had not performed the same activity in a previous or subsequent age-period, they were assigned the median value from the study population.

Statistical analysis

For the total sample, and separately for premenopausal and postmenopausal women in subgroup analyses, PA variables were categorized into 0 and tertiles of non-zero values of MET-hours/week PA if there were adequate controls in the 0 MET-hours/week category. Otherwise, quartiles of mean MET-hours/week of PA based on the distributions of controls were applied to categorize PA types. Univariate logistic regressions were performed with the potential confounding factors, which included: demographic characteristics (age, socio-economic status, remoteness of residence and education attainment); reproductive history (age at menarche, age at first pregnancy, breastfeeding history and oral-contraceptive use in the past 5 years); medical history (family history of breast cancer and use of hormone replacement therapy), and lifestyle risk factors (alcohol consumption, smoking status and current BMI). Variables were later introduced into a multivariate regression model based upon a conservative p-value of <0.25 in the univariate regression models. A backward stepwise variable elimination was applied. Independent variables with $p>0.10$ were removed from the regression model one at a time. Then, effect modification by risk factors were investigated in the analysis. Interactions between PA and family history of breast cancer; parity; BMI and ER status were included in the total PA model. If results indicated significant interaction effects, subgroup analysis were undertaken.

Restricted Cubic Spline (RCS) [35] function (4 knots option) was used to account for the non-linearity in the investigation of risk of breast cancer and recreational physical activities. In these analyses each of the PA variables was entered into the model as a continuous MET-hours/week variable rather than as a categorical variable.

Results

In the BCEES study, 58% eligible cases (1202/2084) and 41% eligible controls (1785/4356) responded to the questionnaire. Overall, controls were slightly older than the cases; and larger proportion of controls were post-menopausal than cases (77% vs 70%). The characteristics of study participants were summarized in Table 1. Compared to controls, cases were less likely to be post-menopausal; have no children and a short breast feeding history; have clear family history of breast cancer; receive mixed-hormone HRT (Table 1). Furthermore, Over 70% diagnosed breast cancer tested ER positive in our study sample.

Table 1: Characteristics of breast cancer cases and controls

Description of PA components

Levels of physical activities are summarized in different dimensions in Table 2. Domain-wise, household and occupational physical activities were the major contributors to total lifetime PA. Recreational PA accounted for around 20% of lifetime PA among all participants. Intensity-wise, light, moderate and vigorous PA accounted for 57%, 31% and 12% of lifetime PA respectively. No significant differences were observed between cases and controls.

Table 2: Summary of physical activity measures by breast cancer case and control status

PA and risk of breast cancer

The results suggested a non-linear association between lifetime total PA and risk of breast cancer. Women who undertook 95 to 130 MET-hours/week/year PA were at lower risk of breast cancer compared with participants in the other categories (Table 3), although these differences were not statistically significant. Higher amounts of PA did not further reduce risk of breast cancer and in fact the point risk estimate increased in the highest group. A similar pattern was observed among post-menopausal women, while increasing levels of lifetime all PA seemed to be associated with slightly higher risk of breast cancer in the pre-menopausal sub-group. However, the trend was not statistically significant.

No significant interactions for lifetime total PA and BMI, parity and family history were observed (Supplementary Table 1). Analysis by ER status was also performed (Supplementary Table 2). The associations were generally stronger among the ER positive breast cancer cases than the ER negative cases. However, no significant dose-response associations were observed in any analysis.

Table 3: Adjusted logistic regression analyses for lifetime total physical activities (recreational, household, occupational and transport) and breast cancer

When taking into account domains of lifetime PA, our analysis did not yield significant associations between risk of breast cancer and either domains or intensity of lifetime PA in the overall analyses. Sub-group analysis of post-menopausal women yielded a significant association between recreational PA and breast cancer risk (Table 4). Medium rather than high amounts of recreational PA were associated with lower risk of breast cancer. Compared to light- and moderate-intensity PA, vigorous-intensity PA was more relevant for reducing breast cancer risk, especially among post-menopausal women (4-13 METs-hour/week) (Table 4). No clear risk reduction was observed in the pre-menopausal subgroup for any domain or intensity and in fact occupational physical activity seemed to be associated with increased risk.

Table 4: Multiple logistic regressions for different domains and intensities of lifetime physical activity and breast cancer for all participants and stratified by menopausal status

We further examined the associations between recreational PA and breast cancer risk using Restricted Cubic Spline (RCS) analyses. The RCS demonstrated a complicated pattern between the amount of lifetime recreational PA and risk of breast cancer. Compared with doing no recreational PA, up to 21 METs hour/week recreational PA was associated with reduced risk of breast cancer (Figure 1). Recreational PA up to 60 METs hour/week yielded no further risk reduction than to 21 METs hour/week, while the extrapolation beyond 60 METs hour/week suggested a continuous risk reduction. However, only a limited number of participants (less than 5%) had than 60 METs hour/week recreational PA. A similar pattern is demonstrated among post-menopausal women with larger risk reduction effects. Significant risk reduction was observed at level up to 20 METS-hours/week among post-menopausal women (Figure 1b).

Figure 1: The dose-response analysis of breast cancer risk and recreational physical activity using multivariate restricted cubit splines in all participants (a) and post-menopausal participants (b)

Further analysis of intensity of recreational PA indicated different patterns of dose-response associations of moderate- and vigorous-recreational PA with risk of breast cancer. A medium amount of moderate or vigorous recreational PA appeared to be associated with lower risk of breast cancer (Table 5). RCS further suggested different dose-response associations between moderate and vigorous intensity recreational PA with risk of breast cancer (Figures 2, 3). Increasing moderate-intensity recreational PA up to 16 METs-hour/week seemed to be associated with lower risk of breast cancer, with stronger effects among post-menopausal women. Higher amounts beyond 16 METs-hour/week were not associated with decreased risk of breast cancer (Figure 2). On the other hand, an increasing amount of vigorous-intensity recreational PA tended to continuously lower breast cancer risk and significant risk reduction was observed when the amount is higher than 40 METs-hour/week (Figure 3).

Table 5: Multiple logistic regressions on the intensity of lifetime recreational physical activity and breast cancer risk stratified by menopausal status

Figure 2: The dose-response analysis of breast cancer risk and moderate-intensity recreational physical activity using multivariate restricted cubit splines in all participants (a) and post-menopausal participants (b)

Figure 3: The dose-response analysis of breast cancer risk and vigorous-intensity recreational physical activity using multivariate restricted cubit splines in all participants (a) and post-menopausal participants (b)

Discussion

This study investigated the dose-response relationship of lifetime physical activity (in terms of domains and intensity) and risks of breast cancer in general and further in pre- and post-menopausal subgroups. Our analyses indicated a small beneficial effect of lifetime PA in reducing risk of breast cancer overall and in the post-menopausal subgroup, but in a non-linear fashion. We found borderline significant risk reduction for recreational PA in general, but not for other domains of PA (household, occupational and transport PA). The association between recreational PA and breast cancer risk was stronger in the post-menopausal subgroup. The analysis regarding intensity of PAs demonstrated that compared to light and moderate-intensity PA, increasing vigorous-intensity PA is more relevant to reducing breast cancer risk, especially among post-menopausal women although this is also a non-linear association. Finally the dose-response analysis of moderate- and vigorous recreational PA demonstrated distinctive dose-response association patterns with breast cancer risk.

We found stronger associations between recreational PA and risk of breast cancer than other domains of PA. One possible explanation for this is exposure misclassification. Household and occupational PA, particularly among women, is generally light-intensity, which is recalled less reliably than moderate- and vigorous-intensity PA.[29, 36] Also, these results corroborate the findings of previous studies that have measured recreational PA and two or more other PA domains[21, 37-45]; these previous studies have generally found that physical activity in the recreational domain confers the largest risk reduction[40-44], although some studies have observed larger risk reductions in the household domain[37, 39, 45]. We did not find any significant associations between transport PA and breast cancer risk. However, approximately 40% of all study participants reported no transport PA and overall it composed less than 3% of lifetime PA. Therefore, the statistical power was low in our analysis. In terms of intensity of PA, our findings are generally consistent with previous research suggesting stronger effects of vigorous-intensity PA in reducing risk of breast cancer than other lower intensity PA.[2] Again, our results demonstrated non-linear associations, especially among post-menopausal women. No clear associations were observed in the pre-menopausal subgroup in our study.

Our analysis of the recreational PA suggested lower risk of breast cancer among women partaking in a medium amount (6-26 MET-hours/week) of recreational PA. The literature seems to suggest a linear correlation between amount of recreational PA and breast cancer. [15, 16, 18] However, there is significant heterogeneity in the measurement of recreational PA in different studies, with the median value varying from 9 to 52 MET-hours/week. [9, 13, 15, 17] Therefore, the results in these studies may not be comparable. We applied Restricted Cubic Spline analysis to further the investigation of the dose-response associations between recreational PA and breast cancer risk. The results confirmed a non-linear association. Significant risk reductions were observed among post-menopausal women undertaking up to 20 MET-hours/week recreational PA. The pattern was consistent with findings of the systematic review of prospective cohort studies, in which a spline demonstrated a relatively linear reduction in breast cancer risk with increasing amount of recreational PA up to12 METs-hours/week.[3] However, the spline did not extend above 12 METs-hours/week. [3] Also, the results were broadly consistent with the recommendations from World Health Organization (WHO) and the World Cancer Research Fund. According to the WHO, 150 minutes of moderate-intensity PA or 75 minutes of vigorous-intensity PA per week is recommended for healthy adults,[24] which is roughly equivalent to 9 MET-hours/week. Our findings are also consistent with the World Cancer Research Fund recommendation of 60 minutes moderate-intensity or 30 minutes vigorous-intensity PA on a daily basis for healthy adults to improve fitness level, which corresponds to approximately 20 MET-hours/week.[23]

Our analysis further suggested different dose-response associations between moderate- (3-6 METs) and vigourous-intensity (>=6 METs) recreational PA with risk of breast cancer respectively. Consistent with other relevant studies, [9, 13, 15, 17] increasing amount of vigorous-intensity recreational PA was associated with a decreasing risk of breast cancer, but with diminishing marginal benefits. Again, the effects were stronger among post-menopausal women. However, the results of moderate recreational PA suggested decreased breast cancer risk was associated with up to 9 MET-hours/week. Increasing amounts of moderate-intensity recreational PA (above 17 METs-hour/week) seemed to be associated with increasing risk of breast cancer. It is possible that the results could be partially attributed to reporting bias, as research suggests that cancer patients may over-report their level of PA compared to controls.[46] Further, since only a small proportion (around 10%) of our study participants self-reported more than 26 MET-hours/week of moderate-intensity recreational PA, the spline projection at higher levels may not be reliable. Finally, a few studies in the literature have investigated the association between moderate-intensity recreational PA and risk of breast cancer.[47, 48] Since different definitions and measures were used in these studies to define moderate-intensity recreational PA, the results were not comparable to ours. Further study is needed to confirm the dose-response correlations between moderate-intensity recreational PA and risk of breast cancer.

Although both the PA guidelines from WHO and the World Cancer Research Fund make the assumption that moderate- and vigorous-intensity PA are interchangable in terms of energy expenditure, with the implication that double amount of moderate-intensity is equivalent to vigorous-intensity PA.[23, 24] Our analysis indicated that moderate and vigorous-intensity recreational PA may not be interchangable in terms of reducing risk of breast cancer. In this study, we found generally stronger associations between PA and risk of breast cancer among post-menopausal than pre-menopausal women. The results are consistent with previous research both epidemiological and biomedical.[2]

Strengths

This study had several strengths. We had a large sample size, and had information about a wide range of potentially confounding variables. We were also able to investigate a number of interaction effects in this study, including family history of breast cancer, parity, BMI and ER status. However, none of these variables yielded significant interactions with physical activity. A further strength was having detailed information about physical activity in four domains and across the lifetime. Finally, our investigation of PA as a continuous variable and the use of restricted cubic spline analyses better inform the potential dose-response relationship between different intensity of recreational PA and breast cancer.

Limitations

Our study may be subject to selection bias considering the relatively low response rates. Differences in age and residential remoteness were found between respondents and non-respondents in cases, and there was an age difference in controls. However, their potential influence on the amount of PA was not clear and unlikely to be substantial. Other limitations are associated with the measurement of physical activities. Self-reported physical activity is subject to reporting bias, especially for PAs in the early age-periods.[36]. A further limitation of this study was the lack of information regarding dietary intake. There are no convincing or probable dietary risk factors for breast cancer however, so it unlikely that controlling for dietary factors would have had a meaningful effect on the observed associations.[49] Finally, we did not have information about progesterone-receptor status or stage of breast cancer for cases, so we were not able to investigate if the association between PA and breast cancer risk varied by these clinical characteristics.

Conclusion

In this study, we found non-linear associations between physical activity and risk of breast cancer. The associations between physical activities and breast cancer risk were stronger in post-menopausal women than pre-menopausal women. Medium amounts of recreational PA among post-menopausal women were associated with lower risk of breast cancer as was vigorous intensity recreational PA. Overall, the results of our study supported PA amount recommendations from the WHO and the World Cancer Research Fund/ American Institute for Cancer Research guidelines for cancer prevention. Finally, our study informs different dose-response associations of moderate- /vigorous-intensity recreational PA with breast cancer risks.

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Conflict of interest

The authors declare that they have no conflict of interest.

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