

Background: Recreational physical activity has been consistently associated with lower breast cancer risk, but there is a need to study the intensity and duration of activity that are critical to reduce the risk. The aim of this study was to examine the influence of moderate and vigorous intensity of recreational physical activity performed at different age periods on breast cancer risk.

Material and methods: The case-control study included 858 women with histological confirmation of invasive breast cancer and 1085 women free of any cancer diagnosis, residents of the region of Western Pomerania, aged 28–79 years. The frequency, duration and intensity of lifetime household, occupational and recreational physical activity, sociodemographic characteristics, reproductive factors, family history of breast cancer, current weight and height, and lifestyle habits were measured using a self-administered questionnaire. Unconditional logistic regression analyses were applied to estimate odds ratios (ORs) and 95% confidence intervals (CIs). The risk estimates were controlled for potential risk factors and lifetime household and occupational activities.

Results: We found a risk reduction for recreational activity done early in life (age periods 14–20, 21–34, 35–50 years), particularly at ages 14–20 and 21–34 years, regardless of intensity. Active women engaging in more than 4.5 hours per week of moderate activity during ages 14–20 years had, on average, a 36% lower risk (OR = 0.64, 95% CI: 0.45–0.89) than women who were never or rarely active. For the women who reported 4.5 hours per week of vigorous activity during this period we found about 64% risk reduction (OR = 0.36, 95% CI: 0.26–0.51). For the period after 50 years of age, recreational activity of moderate or vigorous intensity was not significantly associated with the risk.

Conclusion: Recreational physical activity of moderate or vigorous intensity done during adolescence, early and middle adulthood, particularly at ages 14–20 and 21–34 years, is associated with significantly decreased breast cancer risk.

Key words: breast cancer, physical activity, prevention, age, intensity, case-control study.

Intensity of recreational physical activity in different life periods in relation to breast cancer among women in the region of Western Pomerania

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Introduction

Breast cancer is recognized as the most frequently diagnosed cancer among women worldwide, accounting for 1,383 500 of the total new cancer cases and 458 400 of the total cancer deaths in 2008 [1]. Of these, 692 200 (50%) of the cases and 189 500 deaths (27.4%) occurred in developed countries. Poland is one of the countries with a medium incidence rate; in 2009 it was 15 752 new cancer cases and 5362 cancer deaths in 2010 [2]. The development of breast cancer is regarded as a multifactorial process, which means that the direct causes are unknown. However, most epidemiological findings, laboratory animal and clinical studies have recognized risk factors that increase the likelihood of breast cancer developing. Established risk factors include racial group and ethnic country of birth, old age, family disposition, hormonal factors, mammary lesions, exogenous estrogens, obesity, and sedentary lifestyle [3, 4]. The effect of physical activity, especially recreational, on breast cancer risk was reported by numerous epidemiological studies and analyzed in systematic reviews [5–7]. A recently published review of the epidemiologic evidence reported a 25% average statistically significant risk reduction among physically active women compared to the least active [7]. The association was the strongest for recreational physical activity, ranging from 23% to 65% in findings from case-control studies and from 21% to 39% from cohort studies [5]. However, inconsistent findings have been reported regarding a few aspects of physical activity. So far, the time periods in life in which physical activity is the most protective as well as the optimal dose (intensity, duration, frequency of activity) are unknown. Some authors have presented findings indicating that physical activity of vigorous intensity had the greatest impact on breast cancer [8–10], others that moderate to vigorous activity performed regularly did so [11]. Some studies observed no association between intensity of physical activity and the risk of breast cancer [12, 13]. An expert panel of WCRF and AICR has estimated that physical activity plays a *probable* preventive role against breast cancer in postmenopausal women, while in premenopausal women the evidence is weaker – *limited-suggestive* [14]. Estimation of the impact of physical activity on the breast cancer risk is important regarding the public health recommendation and biological mechanisms. Several hypothesized mechanisms relating physical activity and the risk of breast cancer have been proposed in the epidemiologic literature [for review see, e.g. 7, 15–17]. The most frequently reported implicate: reduction of lifetime exposure to sex steroid hormones [18–21], reduction of exposure to insulin and insulin-like growth factor 1 (IGF-1) [22], increase of circulating sex hormone binding globulin (SHBG) and protein binding of IGF-1 [16]. In addition, regular physical activity with mod-

erate intensity is considered as a modulator of inflammation [16, 23], enhances the immune system, and increases antioxidant enzyme levels in order to prevent oxidative stress caused by reactive oxygen species and free radicals [24]. Moreover, physical activity of vigorous intensity is a mediator for the energy balance through reduction of body weight and body fat loss.

The study was designed specifically to estimate the association between recreational physical activity of varying intensity with special emphasis on the potential effect of time periods (14–20, 21–34, 35–50, > 50 years) in a woman's life.

Material and methods

This case-control study was conducted between January 2003 and May 2007. The study received approval of the Ethics Committee of the Pomeranian Medical Academy in accordance with the Polish Department of Health and Human Services, and all study participants provided written informed consent before the interview. Cases were women aged 28–79 years diagnosed with histologically confirmed invasive breast cancer residing in the region of Western Pomerania. They were identified from the Szczecin Cancer Registry and selected using a random number generator.

Female controls were randomly recruited among the outpatients from ambulatories, clinics, and hospitals located in the region of Western Pomerania and were free of any cancer diagnosis. Controls were frequency matched to the cases by age within 5-year groups and by place of residence. During the study period, 2409 cases were asked to participate in the study, 1187 cases agreed to participate in the study, and 881 of them completed the questionnaire, sent in the study package. Similarly, of the 1615 controls potentially eligible within the age range, 1189 agreed to receive the questionnaire, but 1121 of them completed and returned it. After verification, the final set included 858 (49.3%) cases and 1085 (67.2%) controls. Respondents reported their demographic characteristics, menstrual and reproductive histories, family history of cancer, personal history of breast disease (cases), use of oral contraceptives (OCP), postmenopausal hormonal replacement therapy (HRT) use, habits, and anthropometric measurements. For cases, all data obtained were currently as of the date of cancer diagnosis, and controls were assigned a comparable date. Detailed information on lifetime physical activity from all sources (household, occupational, and recreational) was assessed for each woman using a questionnaire modeled on those of Kriska *et al.* [25] and Friedenreich *et al.* [26] to allow for self-administration. The number of years, months per year, weeks per month, days per week, and hours per day that each activity was performed were reported by study participants. Recreational physical activity was reported separately for four age intervals: ages 14–20, 21–34, 35–50, and over 50 years. For each age period, women reported their participation in each of 43 different sports and exercise activities up to the reference year (the year before diagnosis for the cases and the year before selection for the study for controls). Only regular participation in sports or exercise of at least one hour a week for at least 4 months per year was included in the analysis. Quantitative analysis of intensity of the activity was estimated

using a specific metabolic equivalent (MET) score defined as “the ratio of the metabolic rate associated with a specific activity to the resting metabolic rate”, abstracted from the Compendium of Physical Activities [27]. Examples of intensity codes used in the classification of physical activity levels are as follows: swimming – 6 MET, running – 7.5 MET. Intensity of physical activity was categorized as follows: low intensity (activities under 3 METs), moderate (activities between 3 and 6 METs), and vigorous (above 6 METs). This categorization is commonly used in the subject literature [11]. The variables estimated in this analysis were average hours/week per year spent in recreational activity during considered intervals of age, calculated using the formulae given by Friedenreich *et al.* [26]. Variables were categorized into quartiles according to the distribution of the variables among controls. Odds ratios (ORs) and corresponding 95% confidence intervals (CIs), as a measure of relative risk of breast cancer, were calculated by using unconditional logistic regression and a full assessment of confounding. Tests for a linear trend across ordinal values of categorical variables were conducted by entering physical activity as the continuous variable in statistical models by using a Wald χ^2 value. All the analyses were done using the statistical package STATISTICA 98 (StatSoft Polska, Kraków, Poland), and a *p* value less than 0.05 was considered statistically significant. Odds ratios were adjusted for potential confounders selected a priori: family history of breast cancer in mother, sisters, or daughters (yes, no), education (elementary school, middle school, high school, academy, and above), place of residence (urban/rural), family income average over past 10 years (low, middle, high), marital status (never married, married, widowed/divorced), body mass index (BMI) (≤ 22.5 , $22.6 < 25.0$, $25 < 30$, $\geq 30/\text{kg m}^2$), age at menarche (≤ 12 , 13 , ≥ 14), age at first childbirth (< 22 , $22\text{--}29$, ≥ 30), number of pregnancies (0, 1, 2, ≥ 3), months of breast feeding (0, < 6 , ≥ 6), use of oral contraceptives (never, ever), age at menopause (< 50 , $50\text{--}54$, ≥ 55 years), postmenopausal hormone replacement therapy (HRT) use (never, ever), regular self-examination of breast (no, yes), stress experience (no, yes), smoking status (never smokers, smokers < 10 cigarettes/day, ≥ 10 cigarettes/day), passive smoking (smoking husband: < 20 cigarettes/day, ≥ 20 cigarettes/day), alcohol consumption (never, ≤ 1 drink/week, $2\text{--}4$ drinks/week, ≥ 5 drinks/week), red meat consumption (< 1 serving/week, $1\text{--}2$ servings/week, $3\text{--}4$ servings/week, ≥ 5 servings/week), animal fat consumption (≤ 2 times/week, ≥ 3 times/week), consumption of vegetables, fruits in tertiles: very rarely (≤ 2 servings/week), rarely ($3\text{--}4$ servings/week), and frequently (≥ 5 servings/week, every day, several times daily), screening mammography or ultrasound examination of breast within past 2 years (no, yes). In addition, models were adjusted for household and occupational physical activity and mutually adjusted for other intensity during the same age period. Final models were adjusted for variables that were found to influence the quality of the model fit, and were statistically significant in the multivariate analyses; they are reported in legends of tables. The selection of variables was carried out using the χ^2 test of maximum reliability.

Results

Characteristics of case patients and control subjects, and association of lifestyle and other risk factors with the risk of breast cancer have been previously reported [28]. Briefly, cases did not differ from controls with respect to average age, age at menarche, age at first birth, parity, age at menopause, marital status, frequency of alcohol intake, and HRT use. Compared with controls, cases were less educated, had a higher BMI, reported shorter duration of breast-feeding, were more likely to have had a family history of breast cancer, to be active or passive cigarette smokers, users of oral contraceptive pills, and more frequently experienced psychological stress. The average annual number of hours per week of recreational, household, and occupational physical activity reported by cases over their lifetimes was lower compared with controls. Cases and controls spent a similarly short time in low intensity (< 3 METs) recreational physical activity (about 0.03 hours/week). The difference in recreational physical activity levels of moderate intensity between cases and controls by age periods are shown in Table 1. The statistically significant lowest relative risks observed occurred for activity performed between 14 and 20 years, for which the multivariable-adjusted OR was 0.59 (95% CI: 0.44–0.88) for activity duration 1.7–4.5 hours/week versus never/rarely. A longer term of moderate physical activity did not cause stronger reduction. It is worth noting a highly significant trend of decreasing

risk with increasing duration of activity. Breast cancer risks were also reduced for women in the third tertile of activity during the periods 21–34 and 35–50 years. The tests for a linear trend were significant, but the decreased ORs were significant in the age-adjusted models and for women in the third category of activity (0.8–2.4 and 0.75–2.5 hours/week, respectively) in the multivariable-adjusted models. Recreational physical activity at age over 50 years was not associated with a risk decrease, though the risk was significantly decreased for the highest quartile of activity in an age-adjusted model.

The repeated analyses for this type of activity of vigorous intensity are presented in Table 2. Statistically significant risk reductions were found for activities done during the periods 14–20, 21–34, and 35–50 years in both the age-adjusted and multivariable-adjusted models, similarly as in the case of moderate intensity. The greatest risk reductions for vigorous activity were observed among women who engaged in activity during the periods 14–20 and 21–34 years. Women who were in the highest quartiles of assigned vigorous intensity (> 4.5 hours/week and > 1.8 hours/week) compared with those who reported never/rarely performing vigorous activity experienced 64% and 54% reduction for activity done during the periods 14–20 and 21–34 years (ORs of 0.36 and 0.46, respectively) (p for trends < 0.0001). Women who were in the top tertile of activity between 35 and 50 years had an OR of 0.61 (95% CI:

Table 1. Odds ratios (OR) and 95% confidence intervals (CI) for breast cancer in relation to recreational physical activity of moderate intensity

Age period/risk factor (hours/week per year)	Cases	Controls	Age adjusted OR* (95% CI)	Multivariable adjusted OR** (95% CI)
14–20 years				
never/rarely	489	466	1.00	1.00
< 1.7	169	193	0.85 (0.67–1.09)	0.86 (0.64–1.14)
1.7–4.5	118	216	0.53 (0.41–0.68)	0.59 (0.44–0.80)
> 4.5	82	210	0.37 (0.28–0.49)	0.64 (0.45–0.89)
p for trend			< 0.0001	< 0.00001
21–34 years				
never/rarely	577	599	1.00	1.00
< 0.8	130	163	0.84 (0.65–1.09)	1.02 (0.74–1.39)
0.8–2.4	70	167	0.44 (0.32–0.62)	0.54 (0.38–0.75)
> 2.4	81	156	0.54 (0.40–0.72)	0.84 (0.60–1.19)
p for trend			< 0.0001	< 0.0051
35–50 years				
never/rarely	554	596	1.00	1.00
< 0.75	118	161	0.80 (0.61–1.05)	0.86 (0.62–1.17)
0.75–2.5	96	167	0.62 (0.46–0.84)	0.71 (0.52–0.98)
> 2.5	90	161	0.60 (0.45–0.79)	0.87 (0.62–1.20)
p for trend			< 0.0001	< 0.037
> 50 years				
never/rarely	717	872	1.00	1.00
< 0.8	51	71	0.82 (0.56–1.20)	0.85 (0.54–1.33)
0.8–2.9	48	67	0.83 (0.56–1.23)	0.92 (0.59–1.43)
> 2.9	42	75	0.63 (0.42–0.94)	0.80 (0.51–1.25)
p for trend			0.015	< 0.40

* adjusted for age; ** adjusted for age, BMI, age at first childbirth, number of pregnancies, breast-feeding, family history of breast cancer, active and passive smoking, intake of vitamins, vigorous recreational physical activity, household and occupational physical activity.

Table 2. Odds ratios (OR) and 95% confidence intervals (CI) for breast cancer in relation to recreational physical activity of vigorous intensity

Age period/risk factor (hours/week per year)	Cases	Controls	Age adjusted OR* (95% CI)	Multivariable adjusted OR** (95% CI)
14–20 years				
never/rarely	490	442	1.00	1.00
< 1.7	189	214	0.82 (0.65–1.04)	0.85 (0.65–1.12)
1.7–4.5	112	217	0.47 (0.36–0.61)	0.56 (0.41–0.75)
> 4.5	67	212	0.28 (0.20–0.38)	0.36 (0.26–0.51)
<i>p</i> for trend			< 0.0001	< 0.0001
21–34 years				
never/rarely	628	617	1.00	1.00
< 0.56	107	155	0.69 (0.52–0.90)	0.79 (0.57–1.08)
0.56–1.8	64	157	0.40 (0.29–0.55)	0.47 (0.33–0.77)
> 1.8	59	156	0.40 (0.26–0.50)	0.46 (0.32–0.66)
<i>p</i> for trend			< 0.0001	< 0.0001
35–50 years				
never/rarely	619	680	1.00	1.00
< 0.49	98	136	0.80 (0.60–1.06)	0.79 (0.57–1.09)
0.49–1.74	69	136	0.56 (0.41–0.76)	0.78 (0.55–1.11)
> 1.74	72	133	0.58 (0.43–0.80)	0.61 (0.43–0.86)
<i>p</i> for trend			< 0.0001	0.012
> 50 years				
never/rarely	767	932	1.00	1.00
< 0.52	35	46	0.89 (0.56–1.42)	0.88 (0.52–1.49)
0.52–1.74	31	54	0.68 (0.43–1.08)	0.76 (0.45–1.28)
> 1.74	25	53	0.54 (0.33–0.89)	0.69 (0.39–1.22)
<i>p</i> for trend			0.0031	0.087

* adjusted for age; ** adjusted for age, education level, BMI, age at first childbirth, number of pregnancies, breast-feeding, family history of breast cancer, active and passive smoking, intake of vitamins, moderate recreational physical activity, household and occupational physical activity.

0.43–0.86) and the linear trend was also statistically significant ($p = 0.012$). For the period after 50 years of age recreational physical activity of vigorous intensity was not significantly associated with breast cancer risk ($p = 0.087$); however, the risk was suggestively decreased among the women reporting at least 0.52 hours/week of vigorous activity. As can be seen from Tables 1 and 2, the age- and multivariable-adjusted OR estimates for association of considered levels of recreational activity with breast cancer incidence are often different. Risk reductions were greater in age-adjusted models. After multivariable adjustment and mutually adjusting for other categories of physical activity evaluated in the questionnaire the risks were attenuated.

Discussion

Data analysis shows that recreational physical activity was strongly associated with the reduced risk for breast cancer for activity during youth (14–20 years), 21–34 years and between 35 and 50 years of age. Statistically significant decreases in the risk occurred among women engaged in recreational activity, regardless of assigned intensity (moderate or vigorous). However, the most marked and consistent risk reductions were observed for activities of vigorous intensity during all the above-mentioned age periods. These data show that moderate recreational activity may be sufficient to protect a women against breast carcinogenesis and are consistent with most previous research [9, 13, 29–31]. The

analysis by Patel *et al.* [31] revealed, however, that moderate intensity of activity may be sufficient to reduce the risk of breast cancer in women with lower levels of baseline circulating estrogen. Knowledge that moderate physical activity is sufficient to reduce the risk of breast cancer may be particularly important for public health, as women engage most frequently in activities of lower energy expenditure. Very recent data on physical activity levels in 15 countries of Europe, including Poland, show that only 12.2% of Polish respondents reported a high level of sport and recreational activity and half of the respondents reported very low or no activity [32]. Tehard and co-workers have observed that almost twice as long time of participation in moderate recreational activity is required to obtain a similar risk reduction as participation in high-intensity activity. The authors found a 38% reduction of the risk for women who undertook ≥ 5 hours per week of vigorous recreational activity. Although the mechanisms of the effect of physical activity on the risk of breast cancer are not yet well understood, the findings reported here are consistent with those of two previous investigations [20, 33] that found decreased concentrations of estradiol and its metabolites induced by moderate and vigorous activity. In addition, the study of Di Petro *et al.* [34] suggests that physical activity of vigorous intensity enhances insulin sensitivity.

To our knowledge, only a few studies [8, 35–37] have analyzed both the intensity level and the period of life of recreational activity in relation to the risk of breast cancer. For

example, Dallal *et al.* [8] observed about 20% reduced risk of invasive breast cancer and a 31% reduction in women with an incident carcinoma *in situ*, who reported > 5 hours/week of vigorous recreational activity at ages 25–34 and 35–44 years. The authors also reported a decrease in risk of non-invasive breast cancer linked to vigorous activity at ages 18–24 years, and a lack of reduction in risk for both moderate and vigorous activity performed at ages 45–54 years. In turn, Peptońska *et al.* [36] in a case-control study of Polish women reported a statistically significant decreased risk of breast cancer for combined moderate and vigorous intensity recreational physical activity (MET \geq 4.5) at ages 20–24, 25–29, 30–34, 35–39, 40s, 50s, and 60s among participants achieving at least 12.4 MET-hours/week for these periods except at age 60–69. We found the greatest risk decrease for recreational activity in ages 14–20 years regardless of the intensity. The greatest benefit of recreational physical activity observed in this study during youth, in the time period when increases in sex hormones and accompanying changes in mammary glands occurred, is in accordance with hypothesized hormone-related mechanisms relating physical activity to breast cancer risk. Physical activity can delay menarche and/or change menstrual cycles, thereby reducing lifetime exposure to the mitogenic effects of endogenous estrogens [38]. Other studies have also found a significant decrease in breast cancer risk among women regularly engaged in recreational activity at a young age [reviewed in 5 and 39]. Risk reductions were also observed for activity performed in early adulthood and middle adulthood similarly as in our study [8, 9, 36]. In contrast to a study carried out by Peptońska *et al.* [36], the study by Lee *et al.* [35] and our study found no significant decrease in breast cancer risk for activity after 50 years of age in multivariable models. In this context it is interesting to note that physical inactivity is one of the well-established risk factors for breast cancer and other civilization diseases that can be modified through behavior changes. In addition to the primary preventive role of regular moderate-vigorous physical activity of some cancers, there is growing interest in its use in the treatment and rehabilitation of patients with cancer. Physical activity may reduce fatigue and depression, which are most prevalent among women after mastectomy [40–42]. A role of physical activity in quality of life of women after mastectomy as a means of improving their physical and mental health is beneficial. In addition, regular lifetime physical activity as a main component of lifestyle can also be considered as a helpful factor to cope with the difficulties resulting from the long-lasting illness, e.g. to increase the level of sense of coherence – a crucial factor that allows patients to return to their everyday life [43].

This study should be interpreted within the context of certain limitations, as in most case-control studies, but has several advantages as well.

The most important limitation is that we relied on self-reported physical activity measures, and the overall response rate was lower among cases than among controls who participated in the study. To address this issue of selection bias, the participants were compared with a sample of Polish women aged 20 to 74 years who participated in the case-

control study evaluating risk factors by breast cancer tumor characteristics [3] and the women surveyed by the Chief Central Statistical Office (GUS) as the Polish Population Health Survey [44], on several medical, lifestyle and social characteristics. The participants were found to have several very similar characteristics; therefore despite the relatively low response rates for the cases, the examined group was representative of the base population of women in the region of Western Pomerania. In addition, the strong breast cancer risk reduction observed for vigorous physical activity and a little weaker for moderate activity and consistency with the literature data argue against any strong selection bias. Each method of assessing physical activity may introduce a misclassification bias in the analyses. This limitation was addressed by assessing various types of physical activity, by recording frequency, duration and intensity of each reported activity. However, concerning this point, any misclassification is not likely to be differential because there is still limited awareness of the preventive role of physical activity against breast cancer. Another limitation of this study is that we asked participants to report detailed lifetime physical activity patterns. We tried to reduce the recall bias by collecting information about recreational physical activity performed at four time periods in a woman's life. An additional limitation of this study is a lack of adjustment for energy intake, likely as in most studies.

Strong points of this investigation include a large sample size, histological confirmation of breast cancer, comprehensive measurement of physical activity, and detailed information available on potential confounders.

In conclusion, this study of recreational physical activity and breast cancer found the preventive effect of activity among women engaged in moderate or vigorous activities during adolescence and early and middle adulthood. Although the intensity of the reported recreational physical activity was not a major contributor to the risk reduction but its duration, the greatest risk reduction was observed for vigorous activities. Of the four periods of activity assessed in this paper, the strongest decrease in risk of breast cancer could be achieved by engaging in recreational activity during adolescence and early adulthood.

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