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Research article

Intensity and timing in life of recreational physical activity in relation to breast cancer risk among pre- and postmenopausal women

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Abstract
Regular recreational physical activity has been found to be associated with a decrease in breast cancer risk in women in the majority of epidemiologic studies, but research findings are inconsistent regarding the intensity of activity and timing in life. To address these issues the relations of moderate and vigorous intensity recreational physical activity during ages 14-20, 21-34, 35-50, and over age 50 years to pre- and postmenopausal breast cancer risk were examined. A case-control study of 858 women, with histological confirmation of invasive breast cancer, and 1085 controls, free of any cancer diagnosis, all subjects aged 28-79 years was conducted in the Region of Western Pomerania (Poland). Physical activity was assessed using a self-administered questionnaire with questions on type of activity, duration, frequency, and intensity for each type of activity. Odds ratios (OR) and 95% confidence intervals (CI) of breast cancer associated with physical activity were calculated using unconditional logistic regression. Vigorous physical activity at ages 14-20 and 21-34 years lowered breast cancer risk by at least 35% in premenopausal women and by at least 51% in postmenopausal women for the highest versus lowest quartiles of the activity. The risk was also reduced in postmenopausal women who reported on average more than 1.74 hours per week of vigorous intensity recreational activity in ages >50 years (OR = 0.58; 95%CI = 0.27-0.97; P for trend = 0.013). For moderate activity the relationships remained statistically significant only in postmenopausal women active during ages 14-20 years. The results indicate also a plausible risk reduction among premenopausal women. These results support the hypothesis that recreational activity, particularly done early in life, is associated with a decrease in the invasive breast cancer risk in postmenopausal women. Among premenopausal women, only vigorous forms of activity may significantly decrease the risk.

Key words: Exercise, breast cancer, case-control study, prevention.

Introduction

Overwhelming evidence suggests that physical activity is a means for reducing women's risk of breast cancer, especially among postmenopausal women, but the evidence is weaker in premenopausal women (Friedenreich and Cust, 2008; Monninkhof et al., 2007). The average magnitude of the risk reduction found in case-control and cohort studies was estimated to be about 30% and 20%, respectively (Friedenreich and Cust, 2008). The risk reductions were reported for various types of activities (household, occupational, recreational, transportation), although the greatest risk reductions were found for recreational activity (Monninkhof et al., 2007). Plausible mechanisms through which physical activity may help preventing breast cancer include: reduction of abdominal fat mass, changes in endogenous sex steroid hormones levels, other metabolic hormones and growth factors, modulation of inflammation and the immune system, and a direct effect on the tumor (Coyle, 2008; Fair and Montgomery, 2009; Gleeson, 2007; McTiernan, 2008; Neilson et al., 2009). Most of breast cancer risk factors reported in the literature are related, e.g., to the prolonged exposure of breast tissue to estrogens, such as early menarche, low parity, late menopause, or use of exogenous estrogens. These factors increase the risk while an early first birth, early menopause, and lactation decrease this risk (American Cancer Society, 2008; Key et al., 2001; Pike et al., 1993).

It has been hypothesized by several researchers that the influence of physical activity on breast cancer and other chronic diseases depends on the intensity of activity and the period of life during which a given activity is performed (Friedenreich and Cust, 2008; Neilson et al., 2009; Thune and Furberg, 2001; Warburton et al., 2007). Only few studies have used a measure of lifetime physical activity that is sufficiently comprehensive to address these crucial questions. It has been reported that women who were physically active during adolescence may exhibit a lower risk of breast cancer due to a lower lifetime exposure to sex hormones (Pike, 1993; Tworoger et al., 2007). Findings from epidemiological studies suggest that habitual physical activity patterns in childhood and adolescence are maintained through the life span, and thereby are related to adult health (Alfano et al., 2002; Tammelin et al., 2003). The authors called for further research aimed at elucidating what age period and intensity of physical activity are most critical towards decreasing breast cancer risk. In view of the above results it would be of interest to evaluate what period of women's life and intensity-level of recreational activity are most critical for prevention against pre- and postmenopausal breast cancer. This is the aim of this study. For this purpose a more detailed measure of recreational physical activity in the age ranges: 14-20, 21-34, 35-50 years, and over age 50 years was adopted.

Methods

Cases and controls

This case-control study was carried out during the period between January 2003 and May 2007. The study was approved by the Ethics Committee of the Pomeranian Medical Academy in accordance with the Polish Department of Health and Human Services. All study participants provided written informed consent before the inter-

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view. The invitation and informed consent forms were send by the Regional Oncology Hospital in Szczecin. Case patients were women aged 28-79 years diagnosed with histologically confirmed invasive breast cancer and operated between January 1999 and January 2007, they were identified from the Szczecin Cancer Registry. Eligibility was limited to cases aged less than 80 years, residing in the Region of Western Pomerania and able to complete a self-administered questionnaire. During this study period 3442 cases were identified. Using a computer program the cases (n = 3442) were assigned random numbers. Subsequently, a fixed percentage (70%) of the cases (n = 2409) were selected for this study. Of 2409 cases selected, 239 were deceased, and 193 women were at age ≥80 years. Of the remaining 1977 cases 1187 agreed to participate in the study, 485 did not respond, 128 were too ill, 6 refused, 62 returned a consent without declaration, and 109 could not be located. Women who agreed to participate in the study were sent a 8-page questionnaire in a stamped, preaddressed envelope to complete and return. Of the 1187 cases, 881 (74.2%) completed the questionnaire, 262 (22.1%) did not respond despite two attempts, 13 (1.1%) could not be contacted, and 31(2.6%) had too many missing data. The overall response rate for the cases was 50.6% (881 questionnaires completed out of 1740 eligible and available cases).

Female controls were frequency matched to the cases by age within 5-year age groups and by place of residence (urban, rural). They were free of any cancer diagnosis and aged <80 years. The women were randomly recruited among the out-patients of clinics, the largest hospital in Szczecin, and four hospitals located in the Region of Western Pomerania. Controls were attending when they caught a cold or for health examination (78.6%), treatment for fractures or pain (5.4%), cardiovascular disease (3.1%), back pain (2.8%), or other diseases (skin, eyes, laryngological) (10.1%). We assume that cases and controls are similar because they were recruited from the same type of medical centers with the same insurance status. Of the 1615 controls recruited, 1189 (73.6%) agreed to participate in the study and 426 refused participation because of a lack of interest or privacy. Of these 1189 women, 1121 completed questionnaires. The overall response rate for controls was 69.4% (1121/1615). Finally, data from 858 cases and 1085 controls were analyzed, since information on physical activity collected from 23 cases and 36 controls contained too many missing data.

The average age at entry was 53.3 years (SD, 9.7 years) for breast cancer cases, whereas 54.8 (SD, 9.5 years) for controls.

Data collection

With the exception of clinical data the information used in this study was derived from a self-administered questionnaire. Participants provided information about their demographic and menstrual factors, current weight and height, reproductive history, family history of breast cancer risk, health behaviours, experience of psychological stress, and detailed information on household, occupational and recreational physical activity up to the reference year (the year before diagnosis for the cases and the year before selection into the study for controls). Details about lifetime history of physical activities, in separate sections: household, occupational, and recreational were recorded in a table format using a modified version of Kriska et al. (1990) and Friedenreich and co-workers (1998) questionnaires to allow for self-administration. The frequency and duration of household and outdoor chores and the job held outside the home were assessed separately over the lifetime. In the section of the questionnaire dealing with lifetime recreational physical activity the participants were asked about their leisure time activity during four age intervals: ages 14-20, 21-34, 35-50, and over 50 years. For each age period, women reported their usual frequency and duration of participation in each of 43 different sports and exercise activities. They indicated number of years, months per year, weeks per month, days per week and hours per day for each reported sport/exercise activity. In addition, women were asked to indicate intensity of the particular activity (i.e., self-reported intensity) among defined intensity levels: 1- activities that required minimal effort; 2- activities requiring moderate effort - increasing the heart rate slightly and causing light sweating; 3 – activities causing the increased heart rate and heavy perspiration. For every specific activity a metabolic equivalent (MET) score ("the ratio of the metabolic rate associated with a specific activity to the resting metabolic rate") was assigned using the Compendium of Physical Activities (Ainsworth et al., 1993, 2000). Moderate activity was defined as activity between 3 and 6 METs, and for vigorous activity it was above 6 METs, similar to other authors (Friedenreich et al., 2001). The averages of hours per week per year spent during considered periods of age in physical activity were calculated based on the formulae given by Friedenreich et al. (1998). The dietary assessment section of a questionnaire consisted of 18 main polish-style food groups, with questions on usual frequency intake during a week and portion size for food.

The questionnaire also contained a question: "Did you experience a strong psychological stress, if so, please specify its kind and time of life". The questionnaire included 12 items concerning life events comparable to those of the widely known Holmes and Rahe social readjustment rating scale (Holmes and Rahe, 1967). The following major life events, recorded by each subject: death of a husband, divorce/separation, death of a close family member/friend or personal illness/injury, were considered as the positive experience of psychological stress. The analysis was restricted to the life events occurring at least 4 years before the reference date.

The reproducibility of the self-report of physical activity was examined in the pilot study of 14 cases and 16 controls, 2-3 months later using the same questionnaire. It was found that the Pearson correlation coefficient for the average number of hours per week per year of recreational activity compared for two time periods was 0.88.

Statistical analysis

Odds ratios (ORs) and corresponding 95% confidence intervals (CIs) to estimate the relationship between physical activity and breast cancer risk were calculated by

unconditional logistic regression modeling. Women who were classified as inactive were used as the reference group.

For each analysis the relationship between the individual physical activity measure and breast cancer risk was assessed in two models: an age-adjusted model and a multivariable model with adjustments for age (continuous) and other known risk factors. Potential confounding factors were selected a priori. Variables considered as confounders were: 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, ≥30 $kg \cdot m^{-2}$), age at menarche (≤12, 13, ≥14), age at first childbirth (<22, 22-29, ≥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, 50-54, >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, 2-4 drinks/week, ≥5 drinks/week), red meat consumption (<1 serving/week, 1-2 servings/week, 3-4 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 (3-4 servings/week), and frequently (≥5 servings/week, every day, several times daily), screening mammography or ultrasonic (USG) examination of breast within past 2 years (no, yes). Additionally, models of recreational physical activity were adjusted for household and occupational physical activity and mutually adjusted for intensity during the same age period. Final models included only 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.

Tests for linear trend were undertaken, and dose-response trends in risk were examined by entering physical activity as continuous variables in statistical models by using the Wald χ^2 value (Harrell, 2001). The Pearson correlation coefficients (r) analyzed the inter-relationship of physical activity measures across categories of intensity and time of life as well as the test-retest reliability. All calculations were performed using software STATISTICA 98 (stat Soft Polsca, Krakow, Poland).

Models were run separately for both premenopausal and postmenopausal women. Women were considered to be postmenopausal if they stated that they were postmenopausal and had no menstrual periods or reported that their periods had stopped at least 1 year before their reference date and if they were not taking HRT. Also included in this group were women who reported taking HRT and their current age was 55 years or more. The remaining women were considered as premenopausal. The latter group included also 4 women (with reference date under 42 years) who reported hysterectomy or were taking HRT.

Results

Risk factors for breast cancer stratified by menopausal status among this study sample have been previously reported (Kruk, 2007). The distribution of major breast cancer risk factors in both menopausal subgroups, stratified by case status is summarized in Table 1. Compared with controls, both pre- and postmenopausal cases had earlier menarche and higher frequencies of breast cancer in first degree female relatives. Cases were also more likely to be active and passive smokers, high alcohol and red meat consumers, but less likely to be vegetables and fruits consumers. Cases more frequently experienced psychological stress than controls. Fewer cases than controls reported breast-feeding and a high education level. Postmenopausal cases tended to be heavier than controls and tended to be younger at the birth of their first child. Other characteristics, such as age at study entry, number of pregnancies, and OCP use were similar between cases and controls.

Age-adjusted and multivariable-adjusted odds ratios and 95% confidence intervals of breast cancer according to moderate level and vigorous level of physical activity are shown in Tables 2 and 3. Age – and multivariable – adjusted risk estimates for the relationship of breast cancer risk with moderate and vigorous intensity recreational physical activity differ substantially. Both moderate and vigorous recreational physical activities done during the periods 14-20, 21-34 and 35-50 years showed inverse and statistically significant trends in the age-adjusted analyses in both menopausal subgroups. Adjustment further for other breast cancer risk factors than age, other types of physical activity and other level of intensity during the same age period attenuated the age adjusted risk and often rendered it nonsignificant. Moderate physical activity (Table 2) was significantly associated with reduced breast cancer risk only in postmenopausal women engaged in sports/exercise at ages 14-20, P trend =0.018 (for activity duration 1.7-4.5 hrs/wk *vs* never/rarely multivariate OR = 0.59, 95%CI = 0.38-0.91). For premenopausal women risk decreased with increasing physical activity, although the dose-response trend was not significant (P trend = 0.068) during this period of life. A similar suggestion of decreased risk with higher level of activity was seen during ages 21-34 years among both pre- and postmenopausal women (P trends = 0.074 and 0.063, respectively). No relationship between moderate activity and reduced risk was apparently observed in ages 35-50 years and over age 50 years. In turn, recreational activity of vigorous intensity (Table 3) done during the periods 14-20 and 21-34 years was statistically significantly associated with reduced risk regardless of menopausal status in both age – and multivariable-adjusted models. Among postmenopausal women the maximal reduction of breast cancer risk with activity at ages 14-20 years was of a higher magnitude (74%) (OR = 0.26; 95%CI = 0.15-0.44) than in premenopausal women (35%) (OR = 0.65; 0.95%CI = 0.38-1.12) for the most active women compared with those that reported never/rarely vigorous activity. In contrast, for activity at ages 21-34 years the

Table 1. Baseline characteristics of breast cancer cases and controls in relation to menopausal status.

Variables		Premenopausal women		Postmenopausal women	
		Cases (n=310) %	Controls (n=475) %	Cases (n=548) %	Controls (n=610) %
Age in reference year (yrs)	≤49	75.5	72.5	8.0	6.9
	50-64	24.5	27.5	50.5	53.0
	≥65	0	0	41.6	40.1
Current BMI (kg/m^2)	≤22.5	33.2	31.2	14.2	25.7
	22.6-<25.0	27.1	27.2	23.2	22.6
	25-<30	29.0	32.4	40.3	35.7
	≥30	10.6	9.3	22.3	15.9
Age at menarche	≤12	19.3	5.9	17.9	3.8
	13	27.7	45.0	21.3	32.0
	≥14	53.0	49.1	60.8	64.3
Age at first childbirth	<22	30.3	20.6	32.8	29.5
	22-29	53.2	62.1	52.3	56.2
	≥30	6.1	6.9	4.8	7.7
Number of pregnancies	0	10.0	10.1	10.0	6.5
	1	21.6	21.3	22.1	23.9
	2	50.3	50.3	43.4	44.7
	≥3	18.1	18.3	24.4	24.9
Months of breast feeding	0	10.0	10.1	10.0	6.4
	<6	61.3	42.5	61.3	61.5
	≥6	28.4	47.4	28.5	32.0
Family history of breast cancer	No	88.0	91.2	81.7	93.4
	Yes	12.0	8.8	18.2	6.6
Smoking status, active smokers	Non smokers	43.2	64.2	56.6	69.5
	<10 cigarettes/day	22.3	15.6	16.8	11.8
	≥10 cigarettes/day	34.2	20.2	26.6	18.5
Passive smoking, smoking husband	Non smoker husband	38.4	62.4	44.5	68.8
	<20 cigarettes/day	24.8	18.9	24.3	17.7
	≥20 cigarettes/day	35.2	23.5	25.4	12.5
Alcohol consumption‡	Never	34.8	34.3	46.9	53.8
	≤1 drink/week	42.3	50.5	37.0	37.2
	≥2 drinks/week	22.3	14.9	15.5	8.9
Red meat consumption	≤2 servings/week	69.3	74.1	73.7	66.2
	≥3 servings/week	30.3	18.7	26.1	23.4
Animal fat consumption	≤2 times/week	13.5	19.4	19.3	25.9
	≥3 times/week	86.1	80.6	80.5	73.9
Vegetables consumption	≤4 servings/week	51.0	39.4	49.3	36.7
	≥5 servings/week	48.4	60.4	50.2	62.6
Fruits consumption (included juices)	<5 servings/week	34.0	24.4	35.4	24.7
	≥5 servings/week	66.0	75.4	61.1	74.8
Intake of vitamins	No	22.3	16.0	24.6	14.8
	Yes	77.3	84.0	75.5	85.1
Stress experience	No	47.7	58.3	39.8	51.0
	Yes	52.3	41.7	60.2	49.0
OCP use	No	73.9	81.0	86.9	88.8
	Yes	26.1	18.9	13.1	11.2
HRT	No			62.2	61.0
	Yes			37.8	39.0
Education level	Elementary school	27.1	13.7	32.5	30.8
	Middle school	37.7	34.3	40.5	35.4
	High school (university, academy)	35.2	52.0	27.0	33.8

‡ One alcoholic drink, tin of beer or a small bottle, 125 of vine or 30 g of high-grade alcohols. OCP - oral contraceptive; HRT-hormonal replacement therapy; BMI - body mass index. Due to missing values, some categories do not sum to 100%.

reduction in breast cancer risk was stronger for premenopausal women than postmenopausal women. Premenopausal women with average of >1.8 hours per week of vigorous recreational activity had a 67% decreased risk of breast cancer compared with women with no vigorous activity (OR = 0.33; 95%CI = 0.18-0.62), while postmenopausal women experienced a 51% reduction (OR = 0.49; 95%CI = 0.28-0.83). Vigorous recreational activity at ages 35-50 years did not appear to be associated with breast cancer risk. For exercise at age >50 years, statistically significant reduction in risk was limited to postmenopausal women who averaged more than 1.74 hours per week of vigorous-intensity recreational activity. The numbers of premenopausal women physically active when aged >50 years were too small to allow statistical comparison (3.9% cases and 6.1% controls were engaged in moderate activity and 5.1% and 4.4% - in vigorous activity, respectively). When the analyses were repeated

Table 2. Odds ratios and 95% confidence intervals for breast cancer incidence in relation to moderate recreational physical activity (average hrs/week/year) during four periods of life by menopausal status.

Physical activity	Ages	Premenopausal women Cases	Controls	OR†(95%CI)	OR†† (95%CI)	Postmenopausal women Cases	Controls	OR†(95%CI)	OR†† (95%CI)
Inactive	**14-20**	155	182	1.00	1.00	334	284	1.00	1.00
<1.7		73	101	.83(.57-1.20)	.92(.57-1.47)	96	92	.88(.63-1.23)	.95(.62-1.45)
1.7-4.5		49	99	.57(.38-.85)	.80(.49-1.31)	69	117	.50(.35-.70)	.59(.38-.91)
>4.5		33	93	.39(.24-.60)	.63(.36-1.12)	49	117	.35(.24-.51)	.65(.41-1.03)
P for trend				<.0001	.068			<.0001	.018
Inactive	**21-34**	187	240	1.00	1.00	390	359	1.00	1.00
<.8		59	77	.95(.65-1.41)	1.18(.73-1.92)	71	86	.75(.53-1.07)	1.01(.66-1.54)
.8-2.4		33	81	.52(.33-.81)	.65(.37-1.13)	37	86	.39(.26-.60)	.46(.28-.77)
>2.4		31	77	.49(.31-.78)	.66(.37-1.18)	50	79	.58(.40-.85)	1.06(.64-1.75)
P for trend				.0002	.074			<.0001	.063
Inactive	**35-50**	186	231	1.00	1.00	368	365	1.00	1.00
<.75		44	82	.69(.45-1.04)	.58(.27-.96)	74	79	.94(.66-1.34)	.98(.62-1.54)
.75-2.5		46	83	.71(.47-1.08)	.84(.51-1.39)	50	84	.59(.40-.87)	.64(.39-1.03)
>2.5		34	79	.52(.33-.82)	.79(.46-1.34)	56	82	.67(.46-.97)	1.07(.67-1.71)
P for trend				.0023	.18			.0025	.32
Inactive	**>50**					420	426	1.00	1.00
<.8						49	69	.73(.50-1.09)	.94(.57-1.56)
.8-2.9						42	57	.75(.49-1.15)	.94(.56-1.59)
>2.9						37	58	.65(.42-1.01)	1.02(.58-1.79)
P for trend								.016	.77

OR – odds ratios; CI – 95% confidence interval. † - Adjusted for age. †† Adjusted for age, body mass index, age at first childbirth, parity, breast-feeding, family history of breast cancer, fruits and vegetable consumption, active and passive smoking, household and occupational physical activity, and vigorous recreational activity.

using physical activity expressed as MET-hours per week results were remarkably similar (data not shown).

Positive correlations were observed between moderate and vigorous intensity recreational activity within the same periods of life. The Pearson correlation coefficients for the respective periods of activity, measured in the average hours per week, ranged from 0.13 to 0.31.

Correlations between the physical activity in ages 21-34 years and that in ages 14-20 years were moderate (r = 0.51 for moderate activity and r = 0.61 for vigorous activity). These correlations were weaker for later periods: between ages 14-20 and 35-50 years (r = 0.32 for moderate activity and r = 0.26 for vigorous activity), as well as between ages 14-20 years and over age 50 years (r= 0.17 for moderate activity and r = 0.05 for vigorous activity).

Discussion

In this case-control study we observed a statistically significant decrease in the breast cancer risk associated with increasing duration of vigorous recreational physical

Table 3. Odds ratios and 95% confidence intervals for breast cancer incidence in relation to vigorous recreational physical activity (average hrs/week/year) during four periods of life by menopausal status

Physical activity	Ages	Premenopausal women Cases	Controls	OR†(95%CI)	OR†† (95%CI)	Postmenopausal women Cases	Controls	OR†(95%CI)	OR†† (95%CI)
Inactive	**14-20**	150	162	1.00	1.00	340	280	1.00	1.00
<1.7		72	110	.68(.47-.99)	.81(.55-1.39)	117	104	.93(.68-1.26)	.90(.61-1.33)
1.7-4.5		51	115	.47(.31-.70)	.65(.40-1.05)	61	102	.49(.34-.70)	.55(.35-.86)
>4.5		37	88	.42(.26-.60)	.65(.38-1.12)	30	124	.20(.13-.30)	.26(.15-.44)
P for trend				<.0001	.036			<.0001	<.0001
Inactive	**21-34**	211	225	1.00	1.00	417	392	1.00	1.00
<.56		36	86	.43(.28-.67)	.55(.32-.92)	71	69	.96(.67-1.36)	1.16(.74-1.82)
.56-1.8		36	83	.44(.28-.68)	.50(.30-.85)	28	74	.40(.26-.61)	.60(.34-1.04)
>1.8		27	81	.33(.20-.53)	.33(.18-.62)	32	75	.35(.22-.56)	.49(.28-.83)
P for trend				<.0001	<.0001			<.0001	.037
Inactive	**35-50**	205	260	1.00	1.00	414	420	1.00	1.00
<.49		39	71	.73(.47-1.13)	.68(.41-1.15)	59	65	.91(.63-1.34)	1.00(.60-1.69)
.49-1.74		31	71	.56(.35-.89)	.63(.37-1.08)	38	65	.58(.40-.89)	.72(.42-1.22)
>1.74		35	73	.59(.40-.93)	1.02(.59-1.77)	37	60	.60(.39-.93)	.93(.53-1.61)
P for trend				.0024	.30			.0024	.30
Inactive	**>50**					473	478	1.00	1.00
<.52						32	40	.83(.51-1.34)	.80(.44-1.45)
.5.2-1.74						26	50	.53(.32-.86)	.58(.29-1.16)
>1.74						17	42	.40(.23-.72)	.52(.27-.97)
P for trend								.0001	.013

OR – odds ratios; CI – 95% confidence interval. † - Adjusted for age. †† Adjusted for age, body mass index, parity, breast-feeding, family history of breast cancer, fruits and vegetable consumption, active and passive smoking, household and occupational physical activity, and moderate recreational activity.

activity at ages 14-20 a nd 21-35 years, regardless of the menopausal status, as well as among postmenopausal women in ages over 50 years. Statistically significant decreases in this risk occurred also among postmenopausal women engaged in moderate recreational activities at ages 14-20 years. This may corroborate the suggestion of Patel et al. (2003) that moderate activity may be sufficient to decrease breast cancer risk in women with lower levels of baseline circulating estrogen, but not in women with higher levels of the hormone. The risk reductions found in this study (40-74%) are within the range 20-80% reported by other researchers (Friedenreich and Cust, 2008; Monninkhof et al., 2007). These findings may be directly compared only with three previous studies (Dallal et al., 2007; Peplonska et al., 2008; Peters et al., 2009) that examined both the intensity level and the period of life of long-term recreational physical activity in relation to breast cancer risk. In the California Teachers Study of women aged 20 to 79 years strenuous recreational physical activity performed at ages 25 to 34 years and 35 to 44 years was found to lead to about 20-30% reduced risk (Dallal et al., 2007). The authors also observed a protective effect of vigorous activity at ages 18-24 years limited to noninvasive breast cancer, and a lack of such relationship for both moderate and vigorous activity at ages 45-54 years, and performed in the past 3 years. In a case-control study of Polish women (Peplonska et al., 2008), risk linked to combined moderate and vigorous intensity recreational physical activity at ages 20-24, 25-29, 30-34, 35-39, 40-49, 50-59 was reduced to within the range 13-31%. In contrast to the Polish study (Peplonska et al., 2008) and this study, the prospective NIH-AARP Diet and Health Study, which examined the effect of light and moderate to vigorous physical activity from ages: 15-18, 19-29, 35-39 years, and performed in the past 10 years on postmenopausal breast cancer risk (Peters et al., 2009), found a 16% reduction of the risk for women who undertook >7 hours per week of recent (in the past 10 years) moderate to vigorous intensity physical activity.

A recent review (Friedenreich and Cust, 2008) reported the average reduction of breast cancer risk of about 26% for vigorous and 22% for moderate physical activity. In turn, the prospective study of postmenopausal women (Leitzmann et al., 2008) noted a 16% statistically nonsignificant breast cancer risk reduction of total physical activity limited to activity of vigorous intensity in the cohort as a whole, whereas a 30% significant reduction in women with BMI<25 $kg \cdot m^{-2}$. Other studies (e.g. John et al., 2003; Maruti et al., 2008; Rockhill et al., 1999) did not find a dose-response effect of physical activity intensity or reported a greater breast cancer risk reduction for moderate intensity (Friedenreich et al., 2001) as well as for vigorous intensity of lifetime total physical activity (Kruk, 2009). Considering menopausal status, some recent studies (Dallal et al., 2007; Peplonska et al., 2008; Tehard et al., 2006) reported risk reduction in postmenopausal or older women (>50 years) engaged in vigorous activity, and weaker or no reduction in the case of non-vigorous activity.

Among studies that differentiate between periods of life engaging in physical activity, 19 case-control studies and four cohort studies, reviewed by Lagerros et al. (2004), provided a summary estimate of the relationship between moderate/vigorous recreational activity during adolescence/young adulthood (12-24 years) and the risk of breast cancer. This quantitative review found the summary relative risk, RR = 0.81; 95%CI = 0.77-0.89 from reported RRs of high *vs* low physical activity ranged from 0.2 to 1.4. Note that each one hour of increased recreational activity per week during adolescence caused a further 3% reduction of risk.

Physical activity during adolescence/young adulthood period of life is considered as a very important inhibitor of the sex steroid hormones strongly associated with development of breast cancer (Thune and Furberg, 2001). Considering menopausal status, a weaker consistence (Monninkhof et al., 2007) for the relationship between the adolescent or adult recreational physical activity and premenopausal breast cancer risk has been reported than with postmenopausal breast cancer risk. Similar results have also been observed in the present study.

It is generally maintained that activity level during childhood and adolescence is one of the best predictors of adult physical activity (Kushi et al., 2006). Moreover, the recent literature review (Hallal et al., 2006) has revealed a strong correlation between physical activity in adolescence and physical activity through adulthood. The results of the present study support this observation, namely recreational physical activity at ages 14-20 years is positively correlated with the level of recreational activity in adulthood.

The present data also indicate that the increased levels of recreational physical activity at ages 21-34 years or even over age of 50 years are important in preventing breast cancer. This is in accordance with suggestion of Friedenreich (2001) that benefit of physical activity seems to accumulate over a lifetime. It also should be noted that this study reveals that a higher amount of moderate physical activity at ages 14-20 is associated with significant decrease in postmenopausal breast cancer risk. This finding is especially important since most women prefer usually moderate leisure time physical activity. Additionally, most international physical activity guidelines also support prescriptions of moderate intensity physical activity (3-6 MET) resulting in a total gross energy expenditure of 4.2 MJ per week as sufficient to reduce breast cancer risk (Warburton et al., 2006).

The present study indicates a statistically significant risk reduction for physical activity also at ages >50 years among postmenopausal women who on average performed more than 1.74 hours per week of vigorous intensity recreational activity. This finding agrees with the Canadian Society 2020 guidelines (AICR, 2005) recommending for adults at least 20-30 minutes vigorous intensity physical activity on 3 days per week as the activity dose for breast cancer prevention, in addition to usual activities done daily. Our finding that the higher level of vigorous physical activity affords greater protection from breast cancer development than those of moderate activity is in line with the findings that a greater intensity of activity or a higher level of exercise may be related to more pronounced suppression of sex hormone concentration

(Neilson et al., 2009). Although, the observed greater reduction in the risk by exercise of vigorous intensity may be also due to dose threshold effect or may result from the fact that vigorous activities are most consistently recalled at all ages in epidemiological studies (Ainsworth et al., 1998; Friedenreich et al., 1998; Sallis and Saelens, 2000). It is worthwhile to add that the above mentioned epidemiological findings as well as the data from randomized controlled trials demonstrate that the "dose" of physical activity may be more important than the intensity of activity. It was found that long-term moderate exercise caused significant reduction of serum estrogens and androgens (McTiernan et al., 1999) or body fat loss (Irwin et al., 2003) in postmenopausal women.

The present study has several potential limitations, as well as several advantages. Likewise as most of the case-control studies, selection bias and recall bias may have influenced the findings. The overall response rate was lower among the breast cancer cases than among controls, although, they were comparable to those obtained in other studies (e.g. Marcus et al., 1999) but lower than, for example, in a study of Peplonska et al. (2008). Additionally the relationships between the risk factors and breast cancer observed in women examined recently (Kruk, 2007), which are consistent with those in the subject literature, argue against any strong selection bias. Also, the study cases and controls were very similar in several medical, lifestyle and social characteristics with those in the large population-based study, which evaluated risk factors by breast cancer tumor characteristics (Garcia-Closas et al., 2006). Controls were also compared with a women sample surveyed by Chief Central Statistical Office (GUS) as the Polish Population Health Survey (GUS, 2004). They were found to exhibit average number hours/week of recreational physical activity comparable to those women sampled by GUS. Recall bias was minimized by evaluation of recreational activity during various periods of a woman's life. The next methodologic limitation, i.e. misclassification bias in the evaluation of physical activity, was addressed by assessing various types of lifetime activities (recreational, household, and occupational) and by recording duration, frequency, and self-determined intensity of each type of activity. Any misclassification is likely to be nondifferential because there is still limited awareness of benefits of physical activity in Polish women. Although the questionnaire applied in this study was not directly validated in the studied group of women, its validity has been previously examined by the questionnaire's authors (Friedenreich et al., 1998).

Among the advantages of this study several factors may be mentioned, namely, the large sample size, histological confirmation of breast cancer, and a comprehensive measure of lifetime physical activity from all sources with all components of each activity. In addition, knowledge of self-reported intensity of activity allowed obtaining a greater precision in the intensity estimates using the MET values. Other advantages of this study include detailed information about a broad range of potential confounding variables gathered and considered in statistical analyses. Like John and co-workers (John et al., 2003), this study underlines the importance of control for other factors and potential confounders (among them, other type of activity, a level of intensity or a period of life). For example, the significant OR of 0.59 (adjusted for age) among premenopausal women changed to 1.02 after adjustment for remaining known and suspected risk factors, for time period 35-50 years (Table 3). It is worth mentioning the importance of the finding that risk estimates were similar for both metrics of activity-hours per week and MET-hours per week. Another major strength of the present study is that the applied questionnaire was modeled after that "especially designed to maximize a respondent's ability to report his/her lifetime physical activity patterns" (Friedenreich et al., 1998).

Conclusion

The present study further substantiates the relationship between recreational physical activity and breast cancer risk. We find significant reduction of the risk among postmenopausal women engaged in moderate or vigorous activities during adolescence, early, middle and later adulthood. Premenopausal women experienced significant risk reduction when they were engaged in vigorous activities during adolescence and early adulthood. The reduction in risk among the latter group engaged in moderate activities did not reach significant level. The reduction in invasive breast cancer risk associated with recreational physical activity was stronger for vigorous intensity of activity and higher among postmenopausal women. These results suggest that consistent physical activity during a woman's lifetime is important for the risk reduction. It appears that no critical period exists in which intensity of activities confer the greatest risk reduction. The findings support previous reports of a reduced risk of breast cancer among women physically active during leisure time.

Future studies designed to assess the relationship between the intensity of activity during different periods of life and risk of breast cancer developing could further enhance the findings of the present study. The interventional studies are the most relevant in this regard because they may give valuable information on the effect of exercise on the sex hormones levels and other biomarkers of the risk in difference setting (McTiernan, 2006; Rundle, 2005).

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I state that the typescript of a paper entitled "Intensity and timing in life of recreational physical activity in relation to breast cancer risk among pre- and postmenopausal women" is an original article in the subdiscipline of physical activity and health and declare "no external financial support".

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Key points

- Recreational physical activity of vigorous intensity during ages 14-20 and 21-34 years protect against breast cancer regardless of menopausal status.
- Vigorous recreational physical activity at ages >50 years was also associated with reduced postmenopausal breast cancer risk.
- The risk reduction was also observed among postmenopausal women engaged in recreational physical activity of moderate intensity at ages 14-20 years.

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