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SPORT ACTIVITY AND THE RISK OF BREAST CANCER: RESULTS FROM A CASE – CONTROL STUDY

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Abstract. A case – control study of 257 women with breast cancer and 565 control women was conducted to investigate the effect of life-time sport activity on breast cancer risk. Information was collected by questionnaire about sports played, frequency of participation and duration. The activity levels were determined using frequency variable weighted for metabolic equivalents of energy expenditure (MET). Multivariate logistic regression analyses were used to compute odds ratios (ORs) and 95% confidence intervals (CIs). A full assessment of confounding and effect modification was undertaken. The odds ratios for increasing tertiles of sport activity were 1.00 (referent), 0.50 (CI: 0.33-0.76) and 0.44 (CI: 0.28-0.64), respectively (P-trend = 0.000). Comparing sport active women to inactive women the OR was 0.49 (CI: 0.35-0.69). Models stratified according to body mass index, age at menarche, age at first full term pregnancy, intake of vegetables and fruits, and experience of stress were examined. In models stratified the risks of breast cancer were also reduced with higher levels of activity in sport. The conclusion is that women who participated in sports have a reduced risk of breast cancer.

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Key words: Breast cancer – Sport activity – Case-control study

Introduction

Breast cancer is the most common female cancer in the world and remains the leading cause of cancer death in women [28], but few protective means of preventing the dease, such as lifestyle have been identified [5,21]. For this reason it is important to examine effective lifestyle modifications of preventing the disease, in particular that there is growing number of evidences in so far as increased physical activity may protect against tumor of colon, rectum, lung, prostate, breast and female reproductive tract [2,13,24,31].

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The relationship between physical activity and breast cancer risk has been pointed out by several studies [for review see e.g. 19,20]; the strength of the relationship was found in range from 10% to 70% decrease among women with high levels of physical activity [9,12,23,35,38]. Also a dose response relation (i.e., that the risk decrease is greater when the more activity is performed) was showed in several studies that examined the trend. Not withstanding, in the subject literature we also find increase risk associated with higher levels of physical activity, e.g. three-fold increase in the risk among the most active women was reported by Sternfeld *et al.* [34].

It is well known that prevention strategies are hampered by established risk factors, such as: older age, early age at menarche (≤11 years), nulliparity and late age at first birth (≥30 years), late age at natural menopause (≥55 years) and mutations in genes BRCA 1 and BRCA 2 [17].

The hypothesis that physical activity can reduced the breast cancer risk finds ground from the biological point of view, as the activity has been reported to modulate reproductive hormone levels and menstrual status, helps maintain lower body weight, and may also to augment the defence of the immune system against tumor growth [13,24].

Due to the great need to reduce the breast cancer risk, and since participation in sports and exercise seems to be promising for this purpose a case-control study was conducted to examine wheather participation in sports alters cancer risk of breast cancer. Since the association between physical activity and breast cancer is quite complex, the study was also designed to adjust risk estimates for potential confounders.

Material and Methods

Subjects: A case-control study on breast cancer was conducted between October 1997 and October 1998 in Stettin province. Cases were identified from the Szczecin Regional Cancer Registry. Case subjects were women aged between 35-88 years (median age, 55.0±11.3) after radical mastectomy diagnosed with histologically confirmed incident invasive or in-situ breast cancer and operated in the Szczecin hospitals during 1993-1998. Controls were women aged between 35-93 years (median age, 52.2±12.2) admitted to the hospitals or clinics in the same areas of case subjects. Control subjects were selected to have an age distribution similar to that of the cases; were free of any cancer diagnosis. To increase statistical power, controls were oversampled. The overall response among those who were achievable and provide any information on sport activity were 54.7%

(n=257) cases and 84.3% (n=565) controls. Reason for not obtaining filed questionnaires for cases included: death and illness 15.3%, patient refusal 28.5% and lost to follow-up or moved out of the area (1.5%).

Risk factor questionnaire: All study subjects were asked to complete a structured questionnaire (developed and tested for reliability in a pilot study that preceded the case-control study), including information on socio-demographic characteristics, such as education, occupation and socio-economic indicators; gynaecological factors related to the risk of breast cancer (age at menarche, age at the birth of the first child and total number of full-term pregnancies); anthropometric measures (weight and height); medications taken; diet including vegetables and fruits intake, alcohol intake; experience of stress. The section on sport activity included questions dealing with sports in which women currently participated: basket-ball, hand-ball, volley-ball, athletics, water activities (swimming, sailing, kayaking, rowing), tennis, orienteering, sport gymnastics, running/jogging, skating, participation in a dance group, and conditioning exercises. Information gathered included duration (the number of years spent in sport activity) and the frequency (times per week or month). Women were asked to choose one from several intervals of the number of years sport/training and the number of times per week that the best described their activity.

To study a possible dose-response relationship between the sport activitity and breast cancer risk women were categorized into tertiles of the activity in two separate analyses. The first analyse was based on frequency variable that was weighted for metabolic equivalents of energy expenditure (MET) for each activity. Frequency variable, i.e. appropriate calculation of average number episodes performed per month in earlier period of lifetime was calculated, using the following formula: [(number of years training) x (number of reported times per week sport/training category) x (52 weeks in a year)] / (10 years in time period x 12 months/year). Ten year time period of participation in sports was considered as this was the longest period reported by women and corresponds lifetime period during child/young adulthood. The above given formula is a simple modification of that given by Friedenreich *et al.* [10] for calculations average participation for each activity in a given age / time period.

Daily or 6 times a week training was assigned 7 episodes; 3-5 times-4 episodes once or twice-2 episodes, and less than once a week – 0.5 episode. Engage in sports for 0.5÷1 year was assigned 0.5; 1÷3 years – 2; 3÷5 years – 4; 5÷7 – 6; 7÷9 years – 8, and above 9 years – 10.

The frequency variable was weighted for MET score using Ainsworth *et al.* Compedium of Physical Activities [1]. An MET score classifies specific types of activities as the ratio of metabolic rate to resting metabolic rate. Examples of intensity codes used in calculation are: running (7.5 MET), swimming (6.0 MET), tennis (6.0÷8.0 MET), dancing (4.8 MET), aerobic (6.5 MET), hand-ball (8.0 MET), conditioning exercise (5.5 MET), kayaking (5.0 MET), athletics (6.6 MET) (calculated by averaging the individual MET scores from the activities: running; high jump, long jump; race walking; shot, discus, hammer throw). A total MET score was calculated for various sports weighted by the duration of each activity. For example, a womam active for 2 years in running (MET score of 7.5) and also active for 4 years in aerobic (MET score of 6.5) has a weighted MET score of [(7.5 x 2) + (6.5 x 4)] / 6 = 6.8. The frequency variable weighted for MET for a woman who reported participation in the sports twice a week in this period was calculated as follows: [(6 yrs) x (2 times/wk) x (52 wk/yr)] / [(10 yrs in time period) x (12 mo/yr)] = 5.2 episodes/month over the entire 10-yrs period. A running for 2 years and an aerobic for 4 years have a MET value of 6.8 METs, then (6.8 METs) x (5.2 episodes/month) = 35.4 MET-episodes/month of running and aerobic averaged over the entire 10-yrs period.

The range of the calculated MET-weighted frequency variable among active women (2-108 MET-episodes/month) was divided into three categories of about 35 MET-episodes/month, but clustering in the data did not allow to categorize women basing on percentiles. Regarding the distribution of the data among examined women the sport activity was divided into three levels: the first level *inactive* (women reporting no past sport participation) – they determine the reference category; the second level *low-moderate* active (2÷35 MET-episodes/month), and the third level as *high active* (>35 MET-episodes/month). A distribution of total past training volume among women shows that about 70% of subjects were categorized as inactive or low-moderate active; the classification is comparable with that of other studies [22]. To check the reliability of the above described method of the women categorization the second measure of the sport activity levels was used. In this method *high activity* level is defined when frequency participation in sports was more than 2 times per week, duration (number of years training) ≥5 years and intensity ≥5.5 MET, score. *Low-moderate* level of the activity was defined when all data concerning the sport activity were other than in the case of the *high activity* level. *Inactive* level includes women reporting no past sport participation. This technique categorization has been used by other authors and occurs to be reliable [12,39]. The discrepancy between the two applied method of classification was less than 5%.

Information on sport activity in a later period of lifetime was also gathered but was minimal and incomplete; these data were used as an additional confounder. It was found that addition of this variable to the logistic regression models did not significantly alter the association between the various confounders and risk for breast cancer.

Statistical analysis: Multivariate logistic regression models were used to obtain maximum likelihood estimates of the odds ratios (ORs) and associated 95% confidence intervals (CIs) [4] as well as to evaluate the effects of confounding and modifying factors on the association of sport activity with breast cancer.The variables considered as confounders included age, body mass index (BMI) (weight/height^2), educational level, age at menarche, age at first full-term pregnancy, number of full-term pregnancies, use of hormone replacement therapy, use of oral contraceptives, intake of vegetables and fruits, and experience of stress. There was very little confounding of the past sport activity in these data so most final analysis has been controlled for age (35-44, 45-54, 55-64, >64 years), age at menarche (≤12, 13, ≥14 years), pregnancy (<20, 20-24, 25-29, ≥30 years), BMI (<22, 22-24, >24 kg/m^2), intake of vegetables and fruits (very rarely, rarely, frequently), and experience of stress (yes/no). Statistical analyses were carried out on a PC using statistical package STATISTICA 5.1 ('97 Polish edition). P values for trend were generated using the ordered categorical variables presented in the tables. All P values reported are two-sided, and P values less than 0.05 were considered statistically significant. P values equal to 0.0000 were marked in tables as P=0.

Results

Selected characteristics and breast cancer risk factors among 257 breast cancer cases and 565 control subjects are shown in Table 1. In the study cases were somewhat older than the controls except for women who were 35 to 44 years of age. Age at menarche of 13 years or older was associated with a reduced breast cancer risk, compared with women at age 12 years or younger. A much lower proportion of cases (6.2%) than controls (23.9%) was lean (body – mass index, BMI <22 kg/m^2). Higher BMI were associated with increased risk of breast cancer. Cases reported more frequent experience of stress (OR=3.18, 95% CI: 2.30-4.41 for stress experience yes *versus* no). Women who reported intake of vegetables and fruits frequently compared with reporting very rarely had a risk of breast cancer that was 86% lower (OR=0.14, 95% CI: 0.04-0.48). There was little difference between cases and controls with regard to marital status, education, alcohol ingestion, hormone use (data not shown).

Table 1
Distribution of 257 cases of breast cancer and 565 women controls according to selected characteristics

Variable	Cases N_1 (%)	Controls N_2 (%)	OR (95% CI)	χ^2 (P)
Age group (years)				
35-44	51(19.8)	160(28.3)	1.00*	
45-54	89(34.6)	191(33.8)	1.46(0.97-2.19)	
55-64	56(21.8)	105(18.6)	1.67(1.07-2.63)	
>64	61(23.7)	109(19.3)	1.70(1.13-2.57)	6.4 (P=0.01)
Age at menarche (years)				
≤12	75(29.4)	97(17.2)	1.00*	
13	63(23.9)	129(22.8)	0.63(0.38-0.91)	
≥14	119(46.7)	339(60.0)	0.45(0.31-0.65)	18.6 (P=0.0002)
Age at first full term pregnancy (years)				
<20	25(9.7)	62(11.0)	1.00*	
20-24	134(52.1)	280(49.6)	1.19(0.71-2.00)	
25-29	66(25.7)	137(24.2)	1.14(0.69-1.91)	
≥30	9(3.5)	28(4.9)	0.96(0.50-1.93)	0.01 (P=0.91)
Number of full term pregnancy				
0	23(8.9)	57(10.1)	1.00*	
1-2	196(76.3)	421(74.5)	1.15(0.70-1.92)	
≥3	38(14.8)	87(15.4)	1.04(0.60-1.83)	0.02 (P=0.89)

Table 2
Univariate and multivariate ORs (95% CIs) for breast cancer associated with participation in sport activities

Activity level	Cases Controls N_1/N_2	Univariate OR (95% CI)	Multivariate ORs (95% CIs)	
			[a]OR	[b]OR
1. Inactive	129/163	1.00*	1.00*	1.00*
2. Low-moderate	64/171	0.47(0.33-0.64)	0.45(0.30-0.66)	0.50 (0.33-0.76)
3. High active	64/231	0.34(0.24-0.50)	0.36(0.24-0.52)	0.44 (0.28-0.64)
χ^2 (trend)		34.9 (P=0)	59.2 (P=0)	171.1 (P=0)
1. Inactive	129/163	1.00*	1.00*	1.00*
2. Active	128/402	0.40(0.30-0.55)	0.43(0.31-0.60)	0.49(0.35-0.69)
χ^2 (P)		35.9 (P=0)	102.8 (P=0)	154.0 (P=0)

ORs – odds ratios; CIs – confidence intervals; *denotes reference category:
[a]Adjusted for current age;
[b]Adjusted for categories of current age, age at menarche, age at first term pregnancy, Quetelet's index,
intake of vegetables and fruits, and experience of stress

Table 2 presents findings of the relation between sport activity and breast cancer unadjusted, adjusted only for age ([a]ORs), and multivariate controlling for possible confounding factors ([b]ORs), which were significantly important in the logistic model. Compared with women inactive, the ORs of breast cancer for women low-moderate and high active are 0.50 (95% CI: 0.35-0.76) and 0.44 (95% CI: 0.28-0.64), respectively. The inverse trend in risk was significant (P=0.000). The OR for active women *versus* inactive was 0.49 (95% CI: 0.35-0.69). The ORs unadjusted and adjusted for age were similar to those of the multivariate analysis.

Breast cancer risk associated with sport activity was also examined within tertiles of BMI (<22, 22-24, >24 kg/m^2) (Table 3). Regardless of the level of sport activity, cases were generally heavier than controls. The decreased risk of the breast cancer among women with high activity was stronger in women whose BMI was 22-24 kg/m^2 (OR=0.32, 95% CI: 0.15-0.68). Stratification by age at menarche also revealed some differences. The strongest protective effect of the sport activity was seen for women who began their periods at age 12 years or younger (Table 3), (OR=0.23, 95% CI: 0.09-0.62) for high active *versus* inactive, and strong trends with increasing activity levels were observed (trend P=0.000). The protective effect of sport activity in the case of women who began their periods at age 14 years or older was weaker; risk was reduced 28% for those who were high active. The apparent protective effect of sport activity was significant for women with a first childbirth at age 29 years and less but not for the small group of women with later age (>30 years). The interaction between age at first full term pregnancy and sport activity was not significant (P=0.13, χ^2=9.89, 6 degrees of freedom).

When the data were stratified according to intake of vegetables and fruits, the reduction in risk of breast cancer associated with sport activity was greater for women declaring intake of these products very rarely and rarely than for women declaring an intake frequently (Table 4). Furthermore, the protective effect of sport activity appeared to be stronger among women who did not experience of stress than in women with the stress experience. The interaction was highly statistically significant (P=0.000), but two-sided significance probability for interaction between sport activity and experience of stress did not reach statistical significance (P=0.60, χ^2=1.01, 2 degrees of freedom).

Table 3
Multivariate odds ratios for sport activity of cases and controls by body mass index (BMI), age at menarche, and age at full pregnancy

Activity level	BMI (< 22 kg/m^2)		BMI (22-24 kg/m^2)		BMI (> 24 kg/m^2)	
	N_1/N_2	[a]OR (95% CI)	N_1/N_2	[a]OR (95% CI)	N_1/N_2	[a]OR (95% CI)
1. Inactive	14/55	1.00*	38/44	1.00*	77/64	1.00*
2. Low-moderate active	5/49	0.33(0.09-1.20)	24/56	0.61(0.29-1.30)	35/66	0.47(0.26-0.85)
3. High active	10/90	0.50(0.17-1.50)	17/75	0.32(0.15-0.68)	37/66	0.50(0.28-0.91)
χ^2 (trend)		18.1 (P=0.01)		39.4 (P=0)		59.7 (P=0)

Activity level	Age at menarche					
		≤ 12 years		13 years		≥ 14 years
	N_1/N_2	[b]OR (95% CI)	N_1/N_2	[b]OR (95% CI)	N_1/N_2	[b]OR (95% CI)
1. Inactive	43/25	1.00*	35/44	1.00*	51/94	1.00*
2. Low-moderate active	14/28	0.26(0.09-0.72)	12/28	0.49(0.19-1.20)	38/115	0.73(0.40-1.30)
3. High active	18/44	0.23(0.09-0.62)	16/57	0.28(0.11-0.69)	30/130	0.72(0.39-1.30)
χ^2 (trend)		63.2 (P=0)		54.6 (P=0)		76.7 (P=0)

Activity level	Age at first full term pregnancy							
	< 20 years		20-24 years		25-29 years		≥ 30 years	
	N_1/N_2	[c]OR (95% CI)	N_1/N_2	[c]OR (95% CI)	N_1/N_2	[c]OR (95% CI)	N_1/N_2	[b]OR (95% CI)

Table 4
Odds ratios for sport activity of cases and controls by intake of vegetables and fruits, and experience of stress

Activity level	Intake of vegetables and fruits					
	Very rarely		Rarely		Frequently	
	N_1/N_2	[a]OR (95% CI)	N_1/N_2	[a]OR (95% CI)	N_1/N_2	[a]OR (95% CI)
1. Inactive	42/7	1.00*	41/53	1.00*	46/103	1.00*
2. Low-moderate active	11/13	0.11(0.02-0.52)	19/55	0.38(0.17-0.83)	34/103	0.85(0.48-1.52)
3. Active	5/4	0.07(0.01-0.52)	12/52	0.28(0.11-0.69)	47/175	0.73(0.43-1.20)
χ^2 (trend)		35.6 (P=0)		66.8 (P=0)		58.9 (P=0)

Activity level	Experience of stress			
	No		Yes	
	N_1/N_2	[b]OR (95% CI)	N_1/N_2	[b]OR (95% CI)
1. Inactive	38/84	1.00*	91/79	1.00*
2. Low-moderate active	17/91	0.40(0.19-0.84)	47/80	0.60(0.35-1.02)
3. Active	11/121	0.25(0.11-0.55)	53/110	0.57(0.34-0.95)
χ^2 (trend)		47.5 (P=0)		77.5 (P=0)

OR, odds ratio; CI, confidence interval; N_1, number of cases; N_2, number of controls; *denotes reference category. Estimated were derived from multiple logistic regression equations including for [a]OR current age, age at menarche, age at first full term pregnancy, Quetelet's index, and experience of stress; for [b]OR the multivariate models included the same variables as in case of [a]OR, but the experience of stress variable was replaced by intake of vegetables and fruits. Two-sided significance probabilities for interaction of intake of vegetables, fruits and sport activity χ^2=51.7, 4 df, P=0.000; for interaction of stress χ^2=1.01, 2 df, P=0.60

Discussion

The present results support the hypothesis that sport activity protects women against breast cancer; for women who had ever been engaged in sport activity compared with inactive, sport activity was associated with at least a 50% reduction in their risk. This is consist with the findings of Frisch *et al.* [11], some of recently reported data of Sesso *et al.* [30], and Wyshak and Frisch [38]. Wyshak and Frisch confirmed their earlier findings that former college athletes had a significantly lower risk of breast cancer than nonathletes. They found that the OR for the 15-year incidence of breast cancer is 0.605 (95% CI: 0.438-0.835) among all women. These authors conclude that “athletic activity during the college and pre-college years is protective against breast cancer through the life span, and more markedly among women under 45”.

The results reported here have biological plausibility; controls were leaner, had later menarche; both factors are protective. Early menarche represents more years of exposure to ovarian hormones. There is a considerable amount of evidence suggesting that estrogens and progesterone play a main role in the development of breast cancer [3,31]. Although physical activity exerts diverse physiologic effects through which it could decrease breast cancer risk, the most frequently reported hypothesis is that physical activity may lower the risk via hormonal mechanisms. Many epidemiologic studies have found that physical activity can influence some of factors related to endogenous hormonal profiles, such as age at menarche, number of ovulatory menstrual cycles, and age at menopause [18].

If breast cancer is related to ovarian hormones the observed reduction breast cancer risk with a sport activity may be mediated through a reduction in the total number of ovulation during the life of a woman, therefore women physically active probably have less exposure to estrogens than inactive women. This finds a confirmation in the study of Pirke *et al.* [29] who reported lower estradiol and progesterone levels in their late thens and early twenties among female athletes with and without menstrual disturbances.

Physically active women of all ages are leaner than women more sedentary [33]. It is worth noting that exercise may reduce fat stores – a substrate for transformation of androgens to estrogens [32]. Thune *et al.* [35] found that the greatest reduction of the breast cancer associated with physical activity occurrs among lean women of all ages. Thus, exercise reducing obesity may help maintain the balance in hormone release, and may decrease the endogenous production of estrogens in postmenopausal women, thereby protect women against breast cancer [25,36].

Subgroup analysis showed that the reduction in risk was greater for lean women (BMI <22 kg/m^2) than for women with a higher BMI only in the low-moderate active group (shown in Table 3). A somewhat stronger inverse relation was also seen among high active women who were of average BMI (22-24 kg/m^2), however independly on the BMI value high active and low-moderate active had lower risk than those inactive women. This result is in agreement with the study by Friedenreich *et al.* [9] and Moradi *et al.* [27] of lifetime leisure-time and occupational activities. There is insufficient evidence as yet to reach a conclusion on effect modification by BMI on the dose-response aspects of the relationship between physical activity and breast cancer risk. This situation may be because in some studies stronger reduction of risk for active women was observed for women with low BMI [7,35], while other authors reported these risk decreases more clearly for women whose BMI was high [8] or founding no effect modification of the risk by BMI [6,30].

A higher risk for breast cancer among women with low-medium level of sport activity than those with high level (Table 3) may be due to the validity of data obtained from physical activity questionnaires which is satisfactory for high intensity and sedentary women but worse for a low and moderate levels of activity [16].

Now known previous investigations have reported any effect modification by stress experience or intake of fruits and vegetables on the dependence between sport activity and breast cancer, as was found in this paper. The study was suggested by a new program of the International Agency for Research Cancer, initiated about six years ago, aimed at evaluating a wide range of potential cancer preventive agents and strategies. Prevention strategies of the Unit except for immunological, chemical, and dietery embrace behavioural interventions that may, among others, reduce exposure to underlying risk factors [37]. It was found that sport activity was stronger protective for women having diet poor in fruits and vegetables (Table 4). Several studies [15,26,29,31,37] indicated that diet rich in fruits, vegetables, vegetable oil and/or vitamins having antioxidant properties, such as β-carotene and vitamin E may be protective against breast cancer.

The collected information on sport activity and a stress experience simultaneously in relation to the risk of breast cancer revealed that the effect of sport activity was more pronounced among women who reported that they had never experienced of the strong stress.

In conclusion, this study confirms that sport activity appears to be associated with a reduction in the breast cancer risk. A new findings from the study concerns the importance of sport activity in reduction of breast cancer also in the case of women of which diet was poor in fruits and vegetables or experienced stress.

To explore the interrelationships between physical activity, life-style behaviours, breast cancer factors and breast cancer risk epidemiological and controlled, clinical metabolic studies are needed. Therefore, the present study provides a useful contribution to a still open problem.

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