Physical Activity and Breast Cancer Risk[1]

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Abstract

Data from a multicentric case-control study on breast cancer conducted in Italy were used to analyze the relationship of occupational and leisure-time physical activity with breast cancer risk. Cases were 2569 histologically confirmed incident breast cancer cases, and controls were 2588 patients admitted to the same network of hospitals of cases for acute, nonneoplastic, non-hormone related diseases. After allowance for major identified potential confounding factors (including an estimate of total calorie intake), the odds ratios (ORs) were 0.70, 0.71, 0.64, and 0.54 in subsequent levels of physical activity at work at ages 30–39, compared to the lowest level. The association was similar for occupational physical activity at ages 15–19 and still apparent at ages 50–59, with risk estimates of 0.86, 0.85, 0.85, and 0.62. The ORs for the highest *versus* the lowest category of leisure-time physical activity were also below unity (ORs for the highest level of leisure-time physical activity at ages 15–19, 0.95; at ages 30–39, 0.76; and at ages 50–59, 0.66). The protection of physical activity was apparently stronger below age 60 at diagnosis and was consistent across the strata of selected covariates, although the protection was somewhat greater for more educated women.

Introduction

There are various indirect indications that physical activity can reduce breast cancer risk. These include the observation that strenuous exercise in adolescence is associated with reduced breast cancer risk later in life (1), possibly by delaying menarche and, in general, reducing the frequency of ovulation, which is a possible correlate of a woman's breast cancer risk (2–5).

Only scanty epidemiological data are available on the issue. These include an investigation of athletes (1), indicating a lower prevalence of breast cancer among more active people; a study using occupational status as indicator of physical activity (6), which found decreased breast cancer mortality in more active women; and the First National Health and Nutrition Examination Survey (7), which reported inverse associations for either leisure time and occupational activity, in postmenopausal women only. The Framingham study (8), however, suggested a positive relationship, of borderline significance, for occupational and leisure-time physical activities combined. No adjustment for dietary factors was possible on those data. The First National Health and Nutrition Examination Survey and the Framingham study were both based on relatively few cases of breast cancer (122 and 117, respectively).

Results from a cohort study conducted in Finland on physical education and language teachers were first reported by Vihko (9), and indicated a reduced risk of breast cancer for premenopausal physical education teachers. A subsequent report from the same study (10), however, showed an excess risk of breast cancer in both teacher groups as compared to the total Finnish female population and only a slight difference in breast cancer risk between the two groups. A record-linkage study conducted in Shanghai (11), using occupational categories as proxy indicators of physical activity, found lower standardized incidence ratios for women employed in occupations requiring short time sitting and high energy expenditure, with standardized incidence ratios of 87 for service workers and 91 for craftswomen, and the protection persisted in retired women. A Turkish study (12) found an OR[3] of 1.1 for very low energy expenditure and of 1.5 for long time spent sitting at work, but these associations were weakened after allowance for socioeconomic status.

Only a case-control study conducted within the Cancer Surveillance Program of the University of Southern California (4) on 545 breast cancer cases 40 years of age or under was specifically focused on physical activity. A strong protection emerged with physical activity (OR = 0.42 for women reporting 3.8 h/week or more of physical activity compared to inactive ones), with a consistent trend in risk, and persisted when several confounding factors were taken into account. In that study, the protection was apparently stronger among parous women, and this was interpreted in terms of the ability of physical activity to reduce ovulatory menstrual cycles and days of exposure to estradiol and progesterone in the luteal phase (13).

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[3] The abbreviations used are: OR, odds ratio; BMI, body mass index; CI, confidence interval.

However, the role of physical activity on breast cancer risk in various populations is still largely undefined. Furthermore, it is not clear whether physical activity at different ages or across strata of other covariates has different effects on breast cancer risk.

Because physical activity is one of the few modifiable risk factors for breast cancer (14), it deserves further evaluation. Therefore, we considered data from a large multicentric Italian study on breast cancer, in which information was available on a few indicators of physical activity and major potential confounding factors, including measures of BMI and total calorie intake. Such a case-control design is of interest also because it can provide now-relevant information on breast cancer risk in European populations.

Materials and Methods

A multicentric case-control study on breast cancer has been conducted between June 1991 and February 1994 in six Italian areas: the provinces of Pordenone and Gorizia in northeastern Italy, the urban areas of Milan and Genoa, the province of Forlì in the north of the country, the province of Latina in Central Italy, and the urban area of Naples in the south. Its general design has already been described (15).

Cases were women with incident, histologically confirmed breast cancer diagnosed no longer than 1 year before the interview and with no previous cancers, admitted to the major teaching and general hospitals of the areas under surveillance. A total of 2569 women ages 23–74 years (median age, 55) were included in the present analysis.

Controls were patients admitted to hospitals in the same catchment area of cases for acute, nonneoplastic, nongynecological conditions unrelated to hormonal or digestive tract diseases or to long-term modifications of diet. A total of 2588 women ages 20–74 years (median age, 56) were recruited. The major diagnostic categories were traumas, mostly fractures and sprains (22%); other orthopedic disorders, such as low back pain and disc disorders (33%); acute surgical conditions (15%); eye diseases (18%); and other miscellaneous diseases, such as ear, nose, throat, skin, and dental conditions (12%).

Controls were not individually matched, but frequency matched with cases according to age in five-year groups (i.e. 20–24, 25–29, 30–34, 35–39... to 70–74) and area of residence, within each hospital and study centre (Table 1). Recruitment of controls was simultaneous with that of cases, and both cases and controls were interviewed during hospitalization. On average, about 4% of cases and controls approached for the interview refused to participate.

The same structured questionnaire and coding manual were used in each center, and all interviewers were centrally trained and routinely supervised. Data checking for consistency and reliability was also performed centrally. The questionnaire included information on sociodemographic characteristics, such as education; occupation and socio-economic indicators; lifelong smoking habits; physical activity at various ages; anthropometric measures before diagnosis and weight at various ages; alcohol and coffee consumption; dietary habits investigated through a validated food frequency consumption section; a problem-oriented personal medical history; family history of selected cancers in first-degree relatives; gynecological and reproductive history; and history of use of oral contraceptives, hormone replacement treatment, and female-hormone-containing drugs for other indications.

The section on physical activity included questions on self-reported intensity of activity at work and in leisure time separately. Both types of activity were elicited for three specific periods of life: from 15 to 19, 30 to 39, and 50 to 59 years. For occupational physical activity, the scores ranged between 1 and 5, corresponding to "very tiring," "tiring," "average," "standing," and "mainly sitting." Physical activity in leisure time was defined according to number of h/week of sport and leisure time activity such as walking, gardening, and cycling. The cutoffs were defined as <2, 2–4, 5–7, and >7 h/week.

Table 1 Distribution of 2569 cases of breast cancer and 2588 controls according to sociodemographic and reproductive variables and other selected factors (Italy, 1991–1994)

	Cases		Controls	
	No.	%	No.	%
Age group (yr)				
<45	470	18.3	472	18.2
45–54	772	30.1	694	26.8
55–64	799	31.1	802	31.0
≥65	528	20.6	620	24.0
Education (yr)				
<7	1273	49.6	1592	61.5
7–11	714	27.8	642	24.8
≥12	582	22.7	354	13.7
Age at menarche (yr)				
<13	1123	43.7	1068	41.3
13	594	23.1	568	22.0
≥14	848	33.0	949	36.7
Unknown	4	0.2	3	0.1
Menstrual cycle				
Regular	2420	94.2	2416	93.4
Irregular	149	5.8	172	6.6
Parity (no. of births)				
Nulliparae	401	15.6	380	14.7
1	592	23.0	509	19.7
2	975	38.0	908	35.1
≥3	599	23.3	789	30.5
Unknown	2	0.1	2	0.1
Age at birth of first child (yr)				
<24	693	27.0	961	37.1
24–28	960	37.3	861	33.3
≥29	515	20.1	386	14.9
Menopausal status				
Pre-menopausal or in menopause	988	38.5	843	32.6
Post	1579	61.5	1745	67.4
Unknown	2	0.1		
Age at menopause (yr)				
<48	436	17.0	626	24.2
48–50	466	18.1	512	19.8
≥51	670	26.1	604	23.3
Unknown	7	0.3	3	0.2
BMI				
<23.3	906	35.3	861	33.3
23.3–26.5	836	32.5	857	33.1
≥26.6	827	32.2	870	33.6
History of breast cancer in first-degree relatives				
No	2270	88.4	2453	94.8
Yes	299	11.6	135	5.2
History of benign breast disease				
No	2263	88.1	2346	90.7
Yes	306	11.9	242	9.4
Study center				
Pordenone	1046	40.7	1015	39.2
Milan	585	22.8	623	24.1
Genoa	290	11.3	310	12.0
Forlì	212	8.3	213	8.2
Rome/Latina	178	6.9	178	6.7
Naples	258	10.0	249	9.6

Table 2 Odds ratios and 95% CIs of breast cancer according to different levels of occupational physical activity (Italy, 1991–1994)

Occupational physical activity	No. cases	No. controls	ORs (95% CI)[a]	
			OR1	OR2
At age 15–19	(2569)[b]	(2588)		
1 (very low)	875	677	1[c]	1[c]
2	794	872	0.75 (0.65–0.87)	0.88 (0.76–1.03
3	572	640	0.73 (0.62–0.86)	0.90 (0.76–1.07)
4	293	363	0.69 (0.57–0.84)	0.85 (0.69–1.05
5 (very high)	25	31	0.64 (0.37–1.11)	0.82 (0.47–1.41)
undefined	10	5		
χ^2_1 trend			17.01[d]	2.17
At age 30–39	(2540)	(2527)		
1 (very low)	268	169	1[c]	1[c]
2	578	576	0.70 (0.55–0.88)	0.71 (0.56–0.90)
3	1309	1310	0.71 (0.57–0.89)	0.77 (0.62–1.00)
4	340	411	0.64 (0.50–0.83)	0.70 (0.54–0.91)
5 (very high)	35	47	0.54 (0.33–0.89)	0.60 (0.37–0.98)
undefined	10	14		
χ^2_1 trend			8.80[d]	3.94[d]
At age 50–59	(1730)	(1819)		
1 (very low)	139	118	1[c]	1[c]
2	682	713	0.86 (0.65–1.13)	1.00 (0.76–1.32)
3	669	715	0.85 (0.64–1.13)	1.01 (0.75–1.33)
4	145	162	0.85 (0.60–1.20)	1.05 (0.74–1.46)
5 (very high)	16	23	0.62 (0.30–1.25)	0.75 (0.38–1.52)
undefined	79	88		
χ^2_1 trend			1.41	0.25

[a] Estimates were derived from multiple logistic regression equations including, for OR1, terms for age, center, age at menarche, age at first birth, number of births, menopausal status, age at menopause, calorie intake, previous benign breast disease, and history of breast cancer in first-degree relatives; for OR2, terms for age, center, and education.
[b] Total number of cases and controls are given in parentheses.
[c] Reference category.
[d] $P < 0.05$.

For women with an occupation other than housewife (60% of the overall sample), only activity during working hours was considered. For housewives (about 40% of the overall sample), the work activity score was 3 when they reported doing housework regularly. For the activity rating at work, the self-reported estimate was relative to the average working days; for leisure-time physical activity, the subjects were required to give a mean rating on the whole week. A comparison was made between activity rating and occupation, with specific reference to the period before diagnosis or interview.

Data Analysis. ORs as estimators of relative risks and the corresponding 95% CIs (16) for various levels of occupational and leisure-time physical activity at various ages were derived using unconditional multiple logistic regression, fitted by the method of maximum likelihood (16). Two models were fitted, one including age in five-year groups (i.e. 20–24, 25–29, 30–34, 35–39. . . to 70–74), study center, age at menarche, number of children, age at birth of first child, age at menopause (peri- and premenopause/<48/48–50/≥51 yrs), family history of breast cancer, history of benign breast disease, and estimated total calorie intake. In the second model were included age, center, and education in three categories (<7/7–11/>11 yrs). A model was fitted including, also, terms for BMI (Quetelet index, kg/m^2) before onset of symptoms or diagnosis, but none of the estimates were modified. Hence, BMI was not included in the analyses presented.

Results

Table 1 shows the distribution of cases and controls according to age and selected covariates. Cases were more educated than controls, reported an earlier menarche, tended to have fewer children, and tended to be older at birth of first child. Cases were less frequently postmenopausal than controls and tended to have a later menopause. More cases reported history of benign breast disease and a family history of breast cancer.

The distribution of the study population according to levels of occupational and leisure-time physical activity and the corresponding ORs are given in Table 2. Cases reported less intense occupational physical activity at various ages, but the differences were more marked at younger age. The multivariate ORs were 0.75, 0.73, 0.69, and 0.64 in increasing levels of occupational physical activity at ages 15–19 compared to the lowest one. The association was somewhat stronger at ages 30–39, with ORs of 0.70, 0.71, 0.64, and 0.54 in the subsequent levels, whereas it was apparently weaker, although still apparent, at ages 50–59, with risk estimates of 0.86, 0.85, 0.85, and 0.62. After allowance for age, center, and education, the ORs were 0.82 for the highest level of physical activity at ages 15–19, 0.60 for activity at ages 30–39, and 0.76 for activity at ages 50–59.

The corresponding information on leisure-time physical activity is given in Table 3. Most cases and controls reported very low levels of leisure-time physical activity, about 60% of cases and controls being in the lowest category. Still, the ORs for the highest *versus* the lowest category of leisure-time physical activity were systematically below unity (0.95 for leisure-time physical activity at ages 15–19, 0.76 for leisure-time physical activity at ages 30–39, and 0.66 for leisure-time physical activity at ages 50–59). When allowance was made for age, center, and education, the OR for the highest level of physical

Table 3 Odds ratios and 95% CIs of breast cancer according to different levels of leisure-time physical activity (Italy, 1991–1994)

Leisure-time physical activity	No. cases	No. controls	ORs (95% CI)[a]	
			OR1	OR2
At age 15–19	(2569)[b]	(2588)		
1 (low)	1270	1301	1[c]	1[c]
2	730	726	0.98 (0.86–1.13)	0.95 (0.83–1.09)
3	330	329	0.99 (0.82–1.18)	0.97 (0.80–1.16)
4 (high)	234	229	0.95 (0.77–1.18)	0.94 (0.77–1.16)
undefined	5	3		
χ^2_1 trend			0.18	1.17
At age 30–39	(2540)	(2527)		
1 (low)	1758	1695	1[c]	1[c]
2	532	554	0.88 (0.76–1.02)	0.87 (0.75–1.00)
3	168	170	0.93 (0.74–1.18)	0.91 (0.72–1.15)
4 (high)	77	93	0.76 (0.55–1.05)	0.77 (0.56–1.06)
undefined	5	15		
χ^2_1 trend			3.67	4.32[d]
At age 50–59	(1730)	(1819)		
1 (low)	1275	1356	1[c]	1[c]
2	261	241	1.10 (0.90–1.35)	1.08 (0.89–1.32)
3	85	83	1.11 (0.80–1.54)	1.05 (0.76–1.45)
4 (high)	31	46	0.66 (0.41–1.06)	0.68 (0.40–1.09)
undefined	78	93		
χ^2_1			0.11	1.15

[a] Estimates were derived from multiple logistic regression equations including, for OR1, terms for age, center, age at menarche, age at first birth, number of births, menopausal status, age at menopause, calorie intake, previous benign breast disease, and history of breast cancer in first degree relatives; for OR2, terms of OR1 plus age, center, and education.
[b] Total number of cases and controls are given in parentheses.
[c] Reference category.
[d] $P < 0.05$.

activity at ages 15–19 was 0.94, 0.77 for activity at ages 30–39, and 0.68 for activity at ages 50–59.

Table 4 presents the ORs of breast cancer for three levels of occupational physical activity at ages 30–39, in separate strata of age, education, parity, menopausal status, calorie intake, and BMI compared to the lowest one. The inverse associations were apparently stronger at younger age at diagnosis (*i.e.*, <60 years) and were consistent across the strata of other covariates, except education, because the association was stronger in more educated women.

Discussion

This study found an inverse association between breast cancer risk and various measures of physical activity. The multivariate ORs were between 0.5 and 0.6 for the highest levels of occupational physical activity at various ages. This association was less consistent for leisure-time physical activity, although the ORs for the highest levels were consistently below unity. This weaker association probably reflects the random variation due to the low frequency of leisure-time physical activity in Italian women, and is possibly related to more difficult assessment of exposure in this type of physical activity. No meaningful information was added by a combined score including occupational and leisure-time physical activity.

The protection was clearer for physical activity at younger ages. This may be related to more marked differences in reported physical activity in younger women, or to some specific influence of intense physical activity on menstrual patterns in adolescence and young adulthood.

Allowance for educational level somewhat attenuated the inverse relationship of occupational physical activity with breast cancer risk, but the pattern of risk persisted, although it was somewhat leveled off. Adjustment for education may nonetheless represent an overadjustment because educational level is related to physical activity at work. Lack of physical activity, and particularly of occupational physical activity, in fact, may be a way through which education, strongly associated to cancer risk in the present study, influences the risk of breast cancer.

The inverse association between measures of physical activity and breast cancer risk was consistent across strata of various covariates. In particular, it was similar in parous and nulliparous women. There was some suggestion, however, that the protection conveyed by physical activity was less apparent among older women. If not explainable only through information or recall bias, this pattern of risk may also indicate a long-term attenuation of the protection. In terms of the multistage theory of carcinogenesis (17), this is consistent with a late-stage effect of physical activity, and hence indirectly supports a hormone-related mechanism (17–20). Some interaction was also apparent with education, suggesting a greater influence of physical activity in more educated women, possibly on account of a wider variability of activity among these women.

In biological terms, the association might be explained through menstrual-related effects of high levels of physical activity [*i.e.*, delay in menarche, increase in the period of irregular menstrual cycles during adolescence, and lifelong menstrual irregularities, these being a correlate of anovulatory cycles (2, 3, 13)]. Consequently, physical exercise may reduce the lifetime combined exposure to progesterone and estrogens (13) and, in turn, breast cancer risk (21). The protection deriving also from moderate levels of physical activity might be explained through a lower concentration of sex-hormone-binding globulin, leading to increased availability of peripheral estrogens among inactive women (22).

Table 4 ORs[a] and 95% CIs of breast cancer according to level of occupational physical activity at work at ages 30–39 in strata of selected covariates (Italy, 1991–1994)

	Levels of physical activity at work[b]			
	2	3	4–5 (highest)	χ^2_1 trend
Age (yrs)				
<50	0.62 (0.4–0.9)	0.66 (0.5–0.9)	0.59 (0.4–0.9)	9.81[c]
50–59	0.61 (0.4–1.0)	0.59 (0.4–0.9)	0.55 (0.3–0.9)	4.19[c]
≥60	0.93 (0.6–1.4)	0.98 (0.7–1.5)	0.79 (0.5–1.2)	1.30
Menstrual cycle				
Regular	0.69 (0.5–0.9)	0.71 (0.6–0.9)	0.62 (0.5–0.8)	7.94[d]
Irregular	0.63 (0.2–1.8)	0.49 (0.2–1.3)	0.47 (0.2–1.4)	2.06
Parity				
Parae	0.68 (0.5–0.9)	0.72 (0.6–0.9)	0.61 (0.5–0.8)	6.35[c]
Nulliparae	0.69 (0.5–1.1)	0.54 (0.3–0.9)	0.70 (0.4–1.3)	4.32[c]
Menopausal status				
Premenopausal or in menopause	0.69 (0.5–0.9)	0.67 (0.5–0.9)	0.61 (0.4–0.9)	12.25[c]
Postmenopausal	0.69 (0.5–0.9)	0.73 (0.5–1.0)	0.62 (0.4–0.9)	3.44[c]
Calorie intake				
1st tertile	0.79 (0.5–1.2)	0.81 (0.1–1.2)	0.59 (0.4–0.9)	4.47[c]
2nd tertile	0.57 (0.4–0.9)	0.59 (0.4–0.9)	0.52 (0.3–0.8)	4.44[c]
3rd tertile	0.61 (0.4–0.9)	0.63 (0.4–0.9)	0.64 (0.4–1.0)	1.96
BMI (kg/m²)				
1st tertile	0.76 (0.5–1.0)	0.74 (0.5–1.0)	0.62 (0.4–1.0)	4.30[c]
2nd tertile	0.67 (0.4–1.0)	0.67 (0.4–1.0)	0.60 (0.4–1.0)	3.14
3rd tertile	0.57 (0.3–0.9)	0.65 (0.4–1.0)	0.55 (0.3–0.9)	2.59
Education (yrs)				
<7	0.80 (0.5–1.3)	0.94 (0.6–1.5)	0.93 (0.6–1.5	0.22
7–11	0.87 (0.6–1.3)	1.04 (0.7–1.5)	0.86 (0.5–1.4)	0.38
≥12	0.63 (0.4–1.0)	0.62 (0.4–1.0)	0.48 (0.2–1.2)	10.51[d]

[a] Estimates were derived from multiple regression equations including terms for age, center, age at menarche, age at first birth, number of births, and age at menopause.
[b] Very low level (1) corresponds to the reference category.
[c] $P < 0.05$.
[d] $P < 0.01$.

Physical activity may reduce an individual's body fat, and hence the availability of estrogens in postmenopausal women. On the other hand, a more complex metabolic mechanism is conceivable because the effect of calorie intake may be balanced by energy expenditure due to physical exercise. In this study, however, the association was not significantly stronger in heavier women nor in pre- or peri- *versus* postmenopausal women, nor in women with high calorie intake. Furthermore, allowance for these covariates did not materially modify the overall pattern of risk.

From a methodological point of view, there are specific problems in the assessment of exposure, and particularly in the absence of validation of physical activity. We used a subjective score in the evaluation of physical activity, and no objective quantification of total energy expenditure was possible. There was, however, a good correlation between level of physical activity reported and patient's job title. Validation of physical activity is still an open issue. In a study conducted on a subsample of the Nurses' Health Study (23), values from a short questionnaire on physical activity were reasonably correlated with those from diaries. A study conducted within the Auckland Heart Study (24), comparing a short 3-month recall questionnaire and a 7-day diary, also found satisfactory correlations. Previous studies conducted with various methods gave similarly encouraging results (25–27). Moreover, moderate variability of reported physical activity in this study, especially for leisure-time physical activity (more than 60% of subjects reported low levels), and the small proportions of very active women may have caused a reduction of the power of the study.

With reference to possible sources of bias, this study has all the related limitations and strengths of a typical hospital-based case-control investigation. All admission diagnoses known or potentially related to breast cancer were not included in the comparison group. The choice of controls among various diagnostic categories should have limited selection bias. Orthopedic conditions among controls might be more common in people with manual occupations, but the risk estimates were similar when separate comparison was made with various diagnostic categories of controls. Cases were identified in the major teaching and general hospitals of the areas under surveillance. Participation was almost complete for both cases and controls. Differential recall or information bias between cases and controls is not likely to represent a major problem in this study, given the absence of any public awareness of the beneficial effect of physical activity on breast cancer risk. The hospital setting, moreover, should have assured a similar attitude toward the interview in cases and controls. Potential confounding by several covariates was controlled for in the analyses, but none of them substantially modified the strength of the results.

In conclusion, this study confirms that physical activity is associated with reduced risk of breast cancer. In terms of population attributable risk (28), 36% of breast cancer cases could be prevented by increasing physical activity to the highest level defined in this study. Also, given the limited possibilities for primary prevention of breast cancer, the possibility of avoiding a considerable proportion (which could correspond to about 4000 deaths based on 1991 data in Italy; Ref. 29) of this cancer is of particular interest from a public health standpoint. The issue must, however, be better understood and quantified before we can define programs of intervention in physical activity for reducing an individual's breast cancer risk.

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