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PHYSICAL ACTIVITY AND THE RISK OF BREAST CANCER

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ABSTRACT

Background Because physical activity may affect hormonal concentrations and energy balance, we decided to investigate whether everyday exercise is related to the risk of breast cancer.

Methods During 1974 to 1978 and 1977 to 1983, a total of 25,624 women, 20 to 54 years of age at entry, enrolled in health surveys and answered questionnaires about leisure-time and work activity.

Results During a median follow-up of 13.7 years, we identified 351 cases of invasive breast cancer among the 25,624 women in the cohort. Greater leisure-time activity was associated with a reduced risk of breast cancer, after adjustments for age, body-mass index (the weight in kilograms divided by the square of the height in meters), height, parity, and county of residence (relative risk, 0.63; 95 percent confidence interval, 0.42 to 0.95), among women who exercised regularly, as compared with sedentary women (P for trend=0.04). In regularly exercising women, the reduction in risk was greater in premenopausal women than in postmenopausal women, and greater in younger women (<45 years at study entry) than in older women (≥ 45 years) (relative risk, 0.38; 95 percent confidence interval, 0.19 to 0.79). In stratified analyses the risk of breast cancer was lowest in lean women (body-mass index, <22.8) who exercised at least four hours per week (relative risk, 0.28; 95 percent confidence interval, 0.11 to 0.70). The risk was also reduced with higher levels of activity at work, and again there was a more pronounced effect among premenopausal than postmenopausal women.

Conclusions Physical activity during leisure time and at work is associated with a reduced risk of breast cancer. (N Engl J Med 1997;336:1269-75.)

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gen and progesterone, thereby inhibiting carcinogenesis in the breast.¹²⁻²² Energy balance might also influence the risk of breast cancer. Caloric restriction in rodents reduces the proliferative activity of the mammary glands²³ and inhibits carcinogenesis.^{24,25} However, the effect of energy balance, as indicated by energy intake, body-mass index (the weight in kilograms divided by the square of the height in meters), and energy expenditure, on the risk of breast cancer has not been examined thoroughly in humans.

In this study we evaluated the influence of physical activity, both at work and during leisure time, on the risk of breast cancer in a cohort of 25,624 premenopausal and postmenopausal women. Data on parity, dietary factors, and body-mass index allowed adjustment for potentially confounding factors, and reassessment of physical activity after three to five years gave an indication of the effect of sustained physical activity on the risk of breast cancer.

METHODS

Study Population

From 1974 to 1978, the National Health Screening Service invited people in three counties in Norway (Oppland, Sogn og Fjordane, and Finnmark) to participate in a survey of risk factors for cardiovascular disease. All women who were 35 to 49 years of age and a random sample of 10 percent of those who were 20 to 34 years of age were invited. In four municipalities in Finnmark all women who were 20 to 34 years of age were invited. A comprehensive description of these populations has been published previously.²⁶ A total of 31,556 women were invited to participate, and 28,621 (91 percent) actually did.

All women in this survey as well as a random sample of women who were 20 to 39 years of age were invited to participate in a second survey three to five years later (1977 to 1983). Of these 34,378 women, 31,209 (91 percent) participated.²⁷ This second survey was used as the base line, because no information on parity and dietary factors was collected during the first survey.

Each woman received a written invitation to participate, to-

VIGOROUS physical training¹⁻⁵ and even moderate exercise⁶⁻⁹ can interrupt the menstrual cycle, perhaps by suppressing the pulsatile release of gonadotropin-releasing hormone.^{10,11} This effect of physical activity may lower a woman's cumulative exposure to estro-

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gether with a one-page questionnaire. The participants were asked to answer the questionnaire and bring it to the clinical examination. At screening, trained nurses checked the questionnaire for inconsistencies regarding physical activity and menopausal status, measured weight and height, and collected blood samples.

During screening in the second survey, the participants were asked to fill out a food-frequency questionnaire, to be returned by mail. After one reminder, 25,892 (83 percent) returned the questionnaire. The energy and fat intakes for each woman were derived from the sum of all food consumed. The semiquantitative food-frequency questionnaire that we used has been described in detail and validated.^{28,29}

Assessment of Physical Activity

Self-reported categories of physical activity during leisure hours in the year preceding each survey were assessed when the women entered the study and graded from 1 to 4 according to the participant's usual level of physical activity. A grade of 1 was assigned to those whose leisure time was spent reading, watching television, or engaging in other sedentary activities; a grade of 2 to those who spent at least four hours a week walking, bicycling, or engaging in other types of physical activity; a grade of 3 to those who spent at least four hours a week exercising to keep fit and participating in recreational athletics; and a grade of 4 to those who engaged in regular, vigorous training or participating in competitive sports several times a week. The self-reported level of physical activity during work hours in the preceding year was also graded on a four-point scale. A grade of 1 was assigned to those whose work was mostly sedentary; a grade of 2 to those whose job involved a lot of walking; a grade of 3 to those whose job required a lot of lifting and walking; and a grade of 4 to those engaged in heavy manual labor.

Two identical assessments of leisure-time activity were made at an interval of three to five years, and the results were combined for all groups. Women who reported moderate (grade 2) or regular (grade 3 or 4) exercise during leisure time in the first survey and regular exercise (grade 3 or 4) in the second survey were characterized as being consistently physically active. Women who were sedentary (grade 1) during leisure time in both surveys were characterized as being consistently sedentary. The women who were neither consistently sedentary nor consistently active during leisure time were characterized as being moderately active.

Follow-up and Identification of Cases of Breast Cancer

We followed a total of 25,707 women who had not been given a diagnosis of cancer before our base-line survey (1977 to 1983). We used the participants' national 11-digit personal identification numbers to identify every incident case of breast cancer reported to the Cancer Registry of Norway and Statistics Norway through the end of follow-up (December 31, 1994). A total of 98 percent of the cases were verified histologically. Women in whom cancer developed ($n=72$) or who died ($n=11$) within the first year of the study were excluded from the analyses to account for the possibility that undiagnosed cancer or severe illness might influence the level of physical activity. Through a linkage to the Central Population Register at Statistics Norway, we obtained information concerning the reproductive history of each woman, including the date of birth of each liveborn child through December 31, 1992, and deaths in the cohort through December 31, 1994.

The ultimate study cohort consisted of 25,624 women who participated in both surveys (age range, 20 to 69 years) during 359,930 person-years of follow-up.

Statistical Analysis

Base-line variables were adjusted for age and compared by analysis of covariance. Cox proportional-hazards regression analysis was carried out to investigate the simultaneous effect of physical activity and covariates on the incidence of breast cancer. To calculate the risk of breast cancer, women were observed for the de-

velopment of breast cancer from entry into the study to the date of diagnosis of any cancer, the time of death, or the end of follow-up, whichever event came first. In the analysis, grades 3 and 4 of leisure-time activity were merged because of the small numbers of women with a grade of 4 in both surveys (48 women in the first survey and 57 in the second survey). As a reference group we used women who were sedentary at work or during leisure time.

In the analyses, we adjusted for age at entry (a continuous variable), county of residence, number of children, age at birth of first child, intake of total fat and energy, and body-mass index. Women who reported that they were premenopausal at base line were treated as premenopausal until they reached the age of 50 during follow-up, at which time they were considered postmenopausal. Women who reported that they were postmenopausal at base line were treated as postmenopausal.

Because there were few women with breast cancer who were sedentary both at work and during leisure time, the effect of this combination on the risk of breast cancer could not be analyzed. All significance tests were two-tailed, and the level of significance was set at 5 percent. The analyses were performed with the SAS statistical package version 6.11.

RESULTS

There were 351 incident cases of breast cancer (100 among premenopausal women and 251 among postmenopausal women) among 25,624 women. The mean length of follow-up was 14.0 years (median, 13.7), and the median age at diagnosis was 54.7 years (range, 36.3 to 68.0).

Table 1 gives the base-line characteristics of the participants. Two thirds of the women reported moderate activity during leisure time, whereas 15 percent exercised regularly. Only 14 percent reported being sedentary at work, whereas 20 percent reported lifting and 5 percent reported doing heavy manual labor. Women who reported regularly exercising during leisure time did not differ from women who were inactive during their leisure time with respect to age at entry or number of children, but they tended to be taller and to have a lower body-mass index, a relatively low ratio of total cholesterol to high-density lipoprotein (HDL) cholesterol in serum, lower serum triglyceride levels, and higher HDL cholesterol levels. Women whose work involved lifting or heavy manual labor had a higher body-mass index and more children than those engaged in sedentary work. Energy intake was positively related to physical activity, but the association was more pronounced with work activity than with leisure-time activity.

We analyzed other possible age-adjusted risk factors for breast cancer at base line and found a 28 percent increase in risk for each additional 6 cm of height and a 13 percent reduction in risk for each child. An older maternal age at the birth of a first child was associated with a borderline increase in risk, whereas body-mass index (in the group as a whole or in the subgroups of premenopausal and postmenopausal women), energy intake, and total fat intake did not influence the overall risk of breast cancer (data not shown).

Table 2 shows the relation between the level of

TABLE 1. BASE-LINE CHARACTERISTICS OF THE WOMEN ACCORDING TO THE LEVEL OF PHYSICAL ACTIVITY IN THE 1977–1983 SURVEY.*

CHARACTERISTIC	LEVEL OF ACTIVITY DURING LEISURE TIME			LEVEL OF ACTIVITY AT WORK			
	SEDENTARY (N=4410)	MODERATE (N=17,481)	REGULAR EXERCISE (N=3719)	SEDENTARY (N=3534)	WALKING (N=15,385)	LIFTING (N=5240)	HEAVY MANUAL LABOR (N=1385)
Age at entry (yr)	45.1	45.0	45.4	44.1	45.0	45.4	46.8
Body-mass index	25.5	24.8	24.5	24.3	24.8	25.2	25.6
Height (cm)	161.9	162.7	163.3	163.4	162.5	162.4	162.8
Triglycerides (mg/dl)†	139.9	127.5	124.0	125.8	130.2	130.2	122.2
HDL cholesterol (mg/dl)‡	54.5	56.1	57.3	55.7	55.7	56.5	58.0
Total cholesterol: HDL cholesterol	4.71	4.50	4.34	4.47	4.55	4.51	4.27
Parity							
No. of children	2.7	2.6	2.7	2.1	2.7	2.8	2.9
Mother's age at first birth (yr)	24.2	24.4	24.5	24.6	24.4	24.1	24.6
Daily energy intake (kJ)	5725	5761	5797	5561	5716	5854	6434
Total daily fat intake (g)	55.4	54.8	54.7	52.4	54.6	55.9	61.5
Daily smoking (%)	40.1	34.5	31.6	35.8	35.3	36.4	26.1

*All variables except age were adjusted for age. All values except those for daily smoking are means. Subjects for whom information concerning certain variables was missing are not included.

†To convert values for triglycerides to millimoles per liter, multiply by 0.01129.

‡To convert values for HDL cholesterol to millimoles per liter, multiply by 0.02586.

TABLE 2. ADJUSTED RELATIVE RISK OF BREAST CANCER ACCORDING TO THE LEVEL OF PHYSICAL ACTIVITY DURING LEISURE TIME AND AT WORK IN THE 1977–1983 SURVEY.*

LEVEL OF PHYSICAL ACTIVITY	CASES OF BREAST CANCER	RELATIVE RISK (95% CI)†	CASES OF BREAST CANCER	RELATIVE RISK (95% CI)‡
During leisure time				
Sedentary	66	1.00	65	1.00
Moderate	249	0.98 (0.75–1.28)	245	0.93 (0.71–1.22)
Regular exercise	36	0.67 (0.44–1.00)	36	0.63 (0.42–0.95)
P for trend		0.08		0.04
At work				
Sedentary	62	1.00	61	1.00
Walking	212	0.76 (0.57–1.01)	210	0.84 (0.63–1.12)
Lifting	64	0.66 (0.47–0.94)	63	0.74 (0.52–1.06)
Heavy manual labor	12	0.46 (0.25–0.86)	11	0.48 (0.25–0.92)
P for trend		0.004		0.02

*The sedentary group is the reference group. CI denotes confidence interval. Subjects for whom information concerning certain variables was missing are not included.

†Variables were adjusted for age at entry.

‡Variables were adjusted for age at entry, body-mass index, height, county of residence, and number of children.

leisure-time or work activity and the overall risk of breast cancer. After adjustment for age and with the sedentary group as the reference group, the relative risk of breast cancer was reduced among women whose jobs involved walking, lifting, or heavy manual labor. Adjustments for other factors (body-mass index, county of residence, number of children, and height) in addition to age changed the risk estimates only slightly. Further adjustments for age at first

birth or dietary factors (energy intake, total fat intake, and fiber intake) did not influence our estimates of relative risk and were omitted from the final model. A 52 percent reduction in risk was observed among the women who reported doing heavy manual labor (relative risk, 0.48; 95 percent confidence interval, 0.25 to 0.92). The overall adjusted risk of breast cancer decreased in a dose–response manner with increasing activity level during leisure time

TABLE 3. ADJUSTED RELATIVE RISK OF BREAST CANCER ACCORDING TO MENOPAUSAL STATUS AND THE LEVEL OF PHYSICAL ACTIVITY IN THE 1977–1983 SURVEY.*

LEVEL OF PHYSICAL ACTIVITY	PREMENOPAUSAL WOMEN		POSTMENOPAUSAL WOMEN	
	CASES OF BREAST CANCER	RELATIVE RISK (95% CI)	CASES OF BREAST CANCER	RELATIVE RISK (95% CI)
During leisure time				
Sedentary	20	1.00	45	1.00
Moderate	68	0.77 (0.46–1.27)	177	1.00 (0.72–1.39)
Regular exercise	10	0.53 (0.25–1.14)	26	0.67 (0.41–1.10)
P for trend		0.10		0.15
At work				
Sedentary	22	1.00	39	1.00
Walking	62	0.82 (0.50–1.34)	148	0.87 (0.61–1.24)
Lifting or heavy manual labor	14	0.48 (0.24–0.95)	60	0.78 (0.52–1.18)
P for trend		0.03		0.24

*The sedentary group is the reference group. Variables were adjusted for age at entry, body-mass index, height, county of residence, and number of children. CI denotes confidence interval. Subjects for whom information concerning certain variables was missing are not included.

TABLE 4. ADJUSTED RELATIVE RISK OF BREAST CANCER ACCORDING TO BODY-MASS INDEX AND THE LEVEL OF PHYSICAL ACTIVITY DURING LEISURE TIME IN THE 1977–1983 SURVEY.*

LEVEL OF PHYSICAL ACTIVITY	BODY-MASS INDEX, <22.8		BODY-MASS INDEX, 22.8–25.7		BODY-MASS INDEX, >25.7	
	CASES OF BREAST CANCER	RELATIVE RISK (95% CI)	CASES OF BREAST CANCER	RELATIVE RISK (95% CI)	CASES OF BREAST CANCER	RELATIVE RISK (95% CI)
Sedentary	21	1.00	14	1.00	30	1.00
Moderate	104	1.12 (0.70–1.79)	73	1.09 (0.61–1.93)	68	0.70 (0.46–1.08)
Regular exercise	6	0.28 (0.11–0.70)	14	0.96 (0.45–2.01)	16	0.83 (0.45–1.53)
P for trend		0.02		0.90		0.36

*The sedentary group is the reference group. Variables were adjusted for age at entry, height, county of residence, and number of children. CI denotes confidence interval. Subjects for whom information concerning certain variables was missing are not included.

(P for trend = 0.04). Women who exercised at least four hours a week during leisure time had a 37 percent reduction in the risk of breast cancer (relative risk, 0.63; 95 percent confidence interval, 0.42 to 0.95).

When the group was divided according to menopausal status (Table 3), a consistently inverse association was observed between the level of leisure-time activity and the premenopausal risk of breast cancer; the adjusted relative risk declined to 0.77 (95 percent confidence interval, 0.46 to 1.27) and further to 0.53 (95 percent confidence interval, 0.25 to 1.14) as the level of activity increased (P for trend = 0.10). A weaker association was observed between the level of leisure-time activity and the postmenopausal risk of breast cancer. The inverse association between the level of activity at work and the risk of breast cancer was also pronounced among

premenopausal women; among premenopausal women whose jobs involved lifting or heavy manual labor, the relative risk was 0.48 (95 percent confidence interval, 0.24 to 0.95).

We also divided the cohort into women who were younger than 45 years of age at entry and those who were 45 or older. Among those younger than 45 years at entry for whom data were complete (of whom breast cancer developed in 138; mean age at diagnosis, 48.3 years), the adjusted relative risk declined to 0.80 (95 percent confidence interval, 0.52 to 1.22) and further to 0.38 (95 percent confidence interval, 0.19 to 0.79) as the level of activity during leisure time increased (P for trend = 0.01). The respective adjusted relative risks were 1.03 (95 percent confidence interval, 0.72 to 1.48) and 0.84 (95 percent confidence interval, 0.51 to 1.39) (P for trend =

TABLE 5. ADJUSTED RELATIVE RISK OF BREAST CANCER ACCORDING TO BODY-MASS INDEX AND OVERALL LEVEL OF PHYSICAL ACTIVITY DURING LEISURE TIME IN THE 1974–1978 AND 1977–1983 SURVEYS.*

OVERALL LEVEL OF PHYSICAL ACTIVITY†	ALL WOMEN		BODY-MASS INDEX, <22.8		BODY-MASS INDEX, 22.8–25.7		BODY-MASS INDEX, >25.7	
	CASES OF BREAST CANCER	RELATIVE RISK (95% CI)‡	CASES OF BREAST CANCER	RELATIVE RISK (95% CI)§	CASES OF BREAST CANCER	RELATIVE RISK (95% CI)§	CASES OF BREAST CANCER	RELATIVE RISK (95% CI)§
	Consistently sedentary	29	1.00	13	1.00	7	1.00	9
Moderately active	283	0.90 (0.61–1.32)	112	0.76 (0.43–1.35)	81	0.87 (0.40–1.88)	90	1.14 (0.57–2.27)
Consistently active	34	0.67 (0.40–1.10)	6	0.23 (0.09–0.60)	13	0.83 (0.33–2.09)	15	1.38 (0.60–3.17)
P for trend		0.09		0.002		0.73		0.42

*The sedentary group is the reference group. CI denotes confidence interval.

†Subjects with a consistently sedentary level of activity were classified as sedentary in both surveys (grade 1). Subjects who remained active, reporting moderate (grade 2) or regular (grade 3 or 4) exercise in the first survey and regular exercise (grade 3 or 4) in the second survey, were classified as being consistently active. Subjects were classified as moderately active if they did not meet the criteria for the other two categories.

‡Variables were adjusted for age at entry, body-mass index, height, county of residence, and number of children.

§Variables were adjusted for age at entry, height, county of residence, and number of children.

0.54) among those for whom data were complete who were 45 years of age or older at entry (of whom breast cancer developed in 208; mean age at diagnosis, 58.2 years). These values indicate that physical activity had a protective effect, particularly with respect to the risk of breast cancer before and soon after menopause.

We examined models stratified according to body-mass index (Table 4). Among lean (body-mass index, <22.8), regularly exercising women, the risk of breast cancer was reduced by 72 percent (relative risk, 0.28; 95 percent confidence interval, 0.11 to 0.70). No such association was observed in the middle or upper thirds of body-mass index among regularly exercising women. In models stratified according to both body-mass index and menopausal status, this association was seen among both premenopausal and postmenopausal lean women (data not shown).

In the second survey 61.2 percent of the participants reported the same level of leisure-time activity as in the first survey, 23.5 percent reported an increased level, and 15.3 percent reported a reduced level. By combining these two assessments of leisure-time activity, we observed that the relative risk declined to 0.23 (95 percent confidence interval, 0.09 to 0.60) as the level of sustained activity increased in lean (body-mass index, <22.8) women (P for trend=0.002) (Table 5). This protective effect across increasing levels of sustained leisure-time activity was observed in both lean premenopausal women (relative risk, 0.23; 95 percent confidence interval, 0.06 to 0.88; P for linear trend=0.02) and lean postmenopausal women (relative risk, 0.24; 95 percent confidence interval, 0.06 to 0.96; P for linear trend=0.03).

DISCUSSION

Our results support the idea that physical activity protects against breast cancer, particularly among premenopausal and younger postmenopausal women. Activity during both leisure time and work reduced the overall risk. There was a significant inverse dose-response relation between leisure-time activity and the risk of breast cancer. The protective effect was evident among lean premenopausal and postmenopausal women, and repeated assessment emphasized the preventive effect of physical activity.

The overall reduction in the risk of breast cancer among active women is consistent with findings in other cohort^{15,17} and case-control¹⁹⁻²² studies, but at variance with the findings of a few others.^{30,31} In one of these discrepant studies,³¹ most of the women were older than in the present study and breast cancer was diagnosed mainly among postmenopausal women. In the other,³⁰ physical activity at college was assessed 35 to 70 years before the diagnosis of breast cancer, and no adjustments were made for potential confounding factors. Our finding of a protective effect of work-related activity on the risk of breast cancer is also in agreement with other studies.^{18,32,33}

Precise assessment of physical activity is difficult in a population-based cohort. The accuracy of the levels of leisure-time activity reported on the questionnaire that we used has been validated previously.³⁴⁻³⁶ Since the level of leisure-time activity correlates with the degree of physical fitness,^{34,36} our observation that recreationally active women tended to be leaner than inactive women and had serum lipid profiles associated with regular exercise strengthens the validity of our assessments. Energy intake was also positively

related to both leisure-time and work activities, particularly work activities.

Repeated assessment of leisure-time activity is important in any analysis of the effect of sustained activity on the risk of breast cancer. The protective effect was notable among lean women who were consistently active during their leisure time. In combining the two assessments for each woman, we may also have increased the precision of our assessment of physical-activity levels, but we cannot differentiate the effect of sustained activity from any misclassification.

The population-based approach and the high participation rate in our study reduced selection bias. The almost complete reporting of incident cases of breast cancer also strengthens our results. Age at menarche was not available and could have confounded our results, but this is not likely, since an increased risk of only 4 percent was observed for each year of earlier age at menarche in a similar study population in Norway.³⁷

Information about the use of hormonal contraceptives was not available, although recent meta-analyses suggest that there is only a small increase in the risk of breast cancer among the youngest women who commonly use hormonal contraceptives.³⁸ It is probable that this information would not have confounded our results to any large extent.

How does physical activity influence the development of breast cancer? The propensity to be physically active may be inherited,³⁹ so the genotype may influence both physical activity and the predisposition to breast cancer. Social and cultural influences on exercise and energy balance seem to be more important than genetic factors,^{39,40} which points to leisure-time activity as an independent and modifiable variable with regard to its effect on the risk of breast cancer.

A reduction in the cumulative exposure to cyclic estrogens and progesterone may in part explain the preventive effect of both leisure-time and work activity. Over the long term, vigorous training and moderate leisure-time activity may decrease estradiol and progesterone secretion,^{3,6,41} reduce the length of the luteal phase,^{10,42} induce anovulation,^{7,8,41,43} delay menarche,^{4,5} and cause secondary amenorrhea.^{2,12}

Physical activity influences energy balance, and experimental studies have shown that calorie restrictions inhibit mammary carcinogenesis.^{24,25,44} Anthropometric measures such as height, body-mass index, and weight gain have been used as biomarkers of calorie intake, and increased values have been reported to be risk factors for breast cancer in humans.⁴⁵⁻⁴⁸ A diet involving a high energy intake has also been associated with early age at menarche,^{5,49} and this finding supports the hypothesis that increased net energy may increase the cumulative hormonal levels that are of importance for carcinogenesis of the breast.

Women who were active during leisure time reported only a slightly higher total energy intake than sedentary women, and they tended to be leaner, indicating that their net available energy was lower. The greater protective effect of leisure-time activity against breast cancer in lean women indicates that there may be an optimal energy balance that inhibits mammary carcinogenesis.

Triglycerides are known to displace estradiol from its tight binding to the sex hormone-binding globulin, which is found in low levels in obese women,⁵⁰ and thus triglycerides increase levels of free estradiol. Serum levels of triglycerides were higher in sedentary women than in women who were more active during their leisure time; thus, exposure to estrogen may be greater in inactive women. This underscores the importance of avoiding obesity if physical activity is to have an optimal inhibitory effect on the risk of breast cancer.

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