Physical Activity in Different Periods of Life and the Risk of Breast Cancer: The Norwegian-Swedish Women’s Lifestyle and Health Cohort Study

Karen L. Margolis,1,2 Lorelei Mucci,3 Tonje Braaten,4 Merethe Kumle,4 Ylva Trolle Lagerros,1 Hans-Olov Adami,1,3 Eiliv Lund,4 and Elisabete Weiderpass1,5,6

1Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden; 2Division of Clinical Epidemiology, Hennepin County Medical Center, Minneapolis, Minnesota; 3Department of Epidemiology, Harvard University School of Public Health, Boston, Massachusetts; 4Institute of Community Medicine, University of Tromsø, Tromso, Norway; and 5Finnish Cancer Registry, Helsinki, Finland; and 6Cancer Registry of Norway, Oslo, Norway

Abstract

Background: Physical activity has been found to be associated with decreased risk of breast cancer in postmenopausal women in the majority of epidemiologic studies, but the association is inconsistent in premenopausal women.

Methods: We studied the effect of physical activity at various ages on the incidence of breast cancer in 99,504 women from 30 to 49 years of age at enrollment in the Women’s Lifestyle and Health Study, a prospective population-based cohort study in Norway and Sweden. Physical activity level on an ordinal scale at age 14, age 30, and age at enrollment, participation in competitive sports, as well as information on other covariates was obtained using a self-administered questionnaire. Complete follow-up with data on incident invasive breast cancer and mortality was collected by linkage to national registries. The relation between physical activity and time to breast cancer development was assessed using Cox proportional hazard models, controlling for potential confounders.

Results: During an average 9.1 years of follow-up, there were 1,166 incident breast cancer cases. The mean age of the women was 41 years at enrollment, and the mean age at breast cancer diagnosis was 48 years. Compared to inactive women, women with higher levels of physical activity at enrollment had a similar risk of incident breast cancer (adjusted relative risk, 1.24 for vigorous activity compared with no activity; 95% CI, 0.85-1.82). Physical activity at age 30 or at age 14 also did not afford any significant protection from breast cancer, nor did a consistently high level of activity from younger ages to enrollment.

Conclusion: We did not find evidence of a protective effect of physical activity on breast cancer risk in this group of primarily premenopausal women. (Cancer Epidemiol Biomarkers Prev 2005;14(1):27–32)

Introduction

Of the known and suspected risk factors for breast cancer, physical activity is one of the few that can be modified (1). Physical activity has been found in the majority of published studies to be associated with decreased risk of breast cancer (2, 3). Several biologically plausible mechanisms have been proposed, including decreased estrogen and progesterone levels, enhanced natural immunity, and reduction in levels of insulin and other growth factors (4). Physical activity might also prevent women from weight gain and development of obesity, an established breast cancer risk factor after menopause (2, 5).

There is no consensus on the critical exposure period, intensity, frequency, or consistency of physical activity that might be required to protect against breast cancer. Although studies have examined different populations at various ages and used widely divergent methods to measure physical activity, there is disagreement even among well-designed studies using similar methods (2). However, in contrast to the findings in postmenopausal women, the association of physical activity and breast cancer incidence in premenopausal women is particularly inconsistent between studies (6-11).

We therefore studied the association between physical activity and incident invasive breast cancer over an average of 9.1 years of follow-up in a cohort of women enrolled in the large, population-based prospective Norwegian-Swedish Women’s Lifestyle and Health Cohort Study. At enrollment, 99,504 participants, ages 30 to 49, answered questions about their physical activity levels at age 14, age 30, and age at enrollment, allowing an assessment of the effect of age at exposure and consistency of physical activity.

Materials and Methods

Study Cohort. The present investigation is based on data from the Women’s Lifestyle and Health Study, a prospective cohort study in Norway and Sweden, described in detail previously (12, 13). The study population includes 57,582 Norwegian women from 34 to 49 years of age at recruitment, and 49,259 Swedish women from 30 to 49 years of age, who were monitored with regard to vital status, incident cancer, and emigration from 1991 to 1992. In Norway, the source population was the entire country during that time. The source population in Sweden consisted of all women who were 30 to 49 years old and residents in the Uppsala Health Care Region from 1990 to 1991. Women were randomly selected from the populations within four

Received 3/25/04; revised 6/1/04; accepted 8/16/04.

Grant support: In Norway, the survey was supported by grants from the National Cancer Institute of the U.S. (grant CA 52449), the Norwegian Cancer Society (grant DNK 90180), and the Aker Foundation. In Sweden, the survey was supported by the Swedish Council for Planning and Coordination of Research, the Swedish Cancer Society, STINT (The Swedish Foundation for International Cooperation in Research and Higher Education), Organon, Pharmacia, Medical Products Agency, and Schering-Plough. K.L. Margolis received support from an award from the National Heart, Lung, and Blood Institute (K23 HL03996) and the Aakre Foundation. In Sweden, the survey was supported by grants from the National Cancer Institute of the U.S. (grant CA 52449), the Norwegian Cancer Society (grant DNK 90180), and the Aker Foundation. In Norway, the survey was supported by grants from the National Cancer Institute of the U.S. (grant CA 52449), the Norwegian Cancer Society (grant DNK 90180), and the Aker Foundation.

Requests for reprints: Karen L. Margolis, Berman Center for Outcomes and Clinical Research, Division of Clinical Epidemiology, Hennepin County Medical Center, Suite 440, 825 South 8th Street, Minneapolis, MN 55404. Phone: 612-347-2179; Fax: 612-341-7935. E-mail: margo006@umn.edu.

Copyright © 2005 American Association for Cancer Research.
were considered premenopausal, regardless of age, hystero-
postmenopausal during the follow-up. All other women
bilateral oophorectomy at enrollment were considered
and became active, and those who remained active over
were active and became inactive, women who were inactive
categorized as those who remained inactive, women who
ages 14 and 30, age 14 and enrollment, and between age 30
in moderate, high, or vigorous activity (active) for each time
of physical activity into women who participated in no or
physical activity over time. First, we dichotomized the levels
of education, body mass index (BMI, categorized as <
25.0, 25.0-29.9, 30.0+), height, smoking status (current, past,
or never), alcohol intake (0 drinks per day, < 1, 1 or more),
age at menarche, parity, age at first birth, months of breast-
feeding, oral contraceptive use (current, past, or never),
sister or mother with breast cancer, menopausal status at
enrollment, and country of origin (Norway versus Sweden).
To assess possible effect modification, we first estimated
hazard ratios comparing active versus inactive women, and
stratified models by age at enrollment, menopausal status,
age at breast cancer diagnosis, smoking status, BMI,
education, and country of origin. We then assessed effect
modification on a multiplicative scale by modeling interac-
tion terms and calculating log-likelihood ratio tests to assess
whether interaction terms were significantly different than 0.
Because we do not have information about menopausal
status after the start of follow-up, the age of 50 was chosen
as a proxy to distinguish premenopausal from postmeno-
pausal breast cancer cases, based on the average age at
menopause (approximately at age 50 in Sweden and at age 49 in Norway; refs. 17, 18).

Results

In our cohort of 99,504 women during an average of 9.1
years of follow-up, altogether there were 1,166 incident
invasive breast cancer cases. The annual incidence of breast
cancer in the cohort per 1,000 cases was 1.38 in Norway, 1.18
in Sweden, and 1.29 overall. The mean age at breast cancer
diagnosis was 48.1 years, and 42% of the cancers occurred in
women 50 and older.

Table 1 shows demographic characteristics and breast
cancer risk factors by physical activity level at enrollment
and for the entire cohort. The mean age of the study
participants at enrollment was 41 years, and only 6.9% of
the cohort was postmenopausal at enrollment. More active
women were slightly younger, had lower BMI (<
0.0001), were less likely to smoke (P < 0.0001), consumed
less alcohol, and were more likely to use oral contraceptives.
There were no clear trends across physical activity levels for
energy intake, oral contraceptive use (current, past, or never),
smoking status (current, past, or never), alcohol intake (0 drinks per day, < 1, 1 or more),
age at menarche, parity, age at first birth, months of breast-
feeding, or family history of breast cancer.

Follow-up. Follow-up of the cohort was achieved through
linkages with existing nationwide health registers. Because
each resident in Norway and Sweden is assigned a unique
national registration number, one can link the data from the
cohort with these registers for virtually complete follow-up
with respect to death and emigration. From the total
population registers, we received information on the dates
of death for women who died during the follow-up period,
and dates of emigration for women who moved out of their
respective countries. The population registers were updated
through January 2003 in Norway and through June 2003 for
Sweden. The national cancer registries, established in the
1950s in both countries, provided data on prevalent cancer
cases at cohort enrollment and on incident invasive breast
cancers as well as other cancers diagnosed in the cohort
during follow-up. During the period studied, these registries
are also estimated to be close to 100% complete (14-16).

Cancer Epidemiol Biomarkers Prev 2005;14(1). January 2005
Downloaded from cebp.aacrjournals.org on October 13, 2017. © 2005 American Association for Cancer Research.
Table 1. Demographic and health-related characteristics at enrollment among 99,504 Norwegian and Swedish Participants in the Women’s Lifestyle Health Cohort, by physical activity level at enrollment, 1991 to 1992

<table>
<thead>
<tr>
<th>Physical activity level at enrollment</th>
<th>n (%)*</th>
<th>None, n = 4,730 (4.9%)</th>
<th>Low, n = 15,323 (15.8%)</th>
<th>Moderate, n = 48,694 (50.2%)</th>
<th>High, n = 20,692 (21.3%)</th>
<th>Vigorous, n = 7,569 (7.8%)</th>
<th>Total, N = 99,504</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age at enrollment (y)</td>
<td>41.2</td>
<td>41.0</td>
<td>40.8</td>
<td>40.8</td>
<td>40.5</td>
<td>40.7</td>
<td></td>
</tr>
<tr>
<td>Mean education (y)</td>
<td>11.6</td>
<td>12.5</td>
<td>12.2</td>
<td>12.6</td>
<td>12.1</td>
<td>12.3</td>
<td></td>
</tr>
<tr>
<td>Mean BMI (kg/m²)</td>
<td>24.8</td>
<td>24.0</td>
<td>23.3</td>
<td>22.5</td>
<td>22.2</td>
<td>23.2</td>
<td></td>
</tr>
<tr>
<td>Mean height (cm)</td>
<td>165.9</td>
<td>166.4</td>
<td>166.2</td>
<td>166.6</td>
<td>166.3</td>
<td>166.3</td>
<td></td>
</tr>
<tr>
<td>Current smoker (%)</td>
<td>6.5</td>
<td>7.0</td>
<td>5.0</td>
<td>5.6</td>
<td>5.1</td>
<td>5.5</td>
<td></td>
</tr>
<tr>
<td>Consume 1+ alcoholic drinks per day (%)</td>
<td>13.1</td>
<td>13.1</td>
<td>13.1</td>
<td>13.2</td>
<td>13.1</td>
<td>13.1</td>
<td></td>
</tr>
<tr>
<td>Age at menarche (y)</td>
<td>14.1</td>
<td>11.0</td>
<td>11.3</td>
<td>11.9</td>
<td>12.8</td>
<td>11.9</td>
<td></td>
</tr>
<tr>
<td>Nulliparous (%)</td>
<td>24.1</td>
<td>24.9</td>
<td>24.8</td>
<td>24.7</td>
<td>24.4</td>
<td>24.8</td>
<td></td>
</tr>
<tr>
<td>Mean breast-feeding (months)</td>
<td>10.6</td>
<td>12.0</td>
<td>12.2</td>
<td>13.0</td>
<td>12.5</td>
<td>12.3</td>
<td></td>
</tr>
<tr>
<td>Family history of breast cancer in sister/mother (%)</td>
<td>5.2</td>
<td>5.1</td>
<td>4.8</td>
<td>5.0</td>
<td>4.9</td>
<td>4.9</td>
<td></td>
</tr>
<tr>
<td>Current users of oral contraceptives (%)</td>
<td>6.5</td>
<td>6.4</td>
<td>8.7</td>
<td>7.3</td>
<td>8.9</td>
<td>8.2</td>
<td></td>
</tr>
<tr>
<td>Postmenopausal (%)</td>
<td>9.7</td>
<td>6.6</td>
<td>7.5</td>
<td>6.0</td>
<td>6.3</td>
<td>6.9</td>
<td></td>
</tr>
<tr>
<td>Norwegian (%)</td>
<td>56.9</td>
<td>67.9</td>
<td>50.2</td>
<td>50.2</td>
<td>51.3</td>
<td>51.7</td>
<td></td>
</tr>
</tbody>
</table>

*Among 97,008 with data on physical activity at enrollment.


discussion

Our data from a large prospective cohort study of primarily premenopausal women do not show any evidence that physical activity in adult life reduces the risk of breast cancer occurring in the first decade of follow-up. There was also no evidence of benefit from physical activity done at younger ages, or from a consistently high level of activity. More specifically, our results pertain to physical activity assessed before age 50 and to breast cancer diagnosed before age 60, but primarily in premenopausal women. Risk estimates seemed largely unconfounded by other established breast cancer risk factors. There was some evidence of effect modification by menopausal status at enrollment, but this was of borderline statistical significance.

A large number of epidemiologic studies have now examined the association between physical activity and the risk of breast cancer. When these were recently reviewed, 8 of 14 cohort studies, and 14 of 19 case control studies observed an inverse association between physical activity and breast cancer incidence (2). Nine of the cohort studies measured leisure time physical activity, either alone or in addition to occupational physical activity (6-8, 19-24). In this review, no clear pattern of risk by menopausal status at the time of measurement of physical activity or at cancer incidence was evident. The Iowa Women’s Health Study enrolled exclusively postmenopausal women, and found no association between physical activity and breast cancer (21), whereas several other smaller studies with primarily postmenopausal cancer cases found a protective effect of physical activity (20, 22). In a population-based Norwegian study, risk of breast cancer was reduced at higher levels of physical activity and the effect was at least as large in premenopausal women and women under age 45 (6). The Nurses’ Health Study, with the largest number of cases, found an approximately 20% reduction in breast cancer risk in the highest category of physical activity, and also reported similar findings in both premenopausal and postmenopausal...
women (8). However, the Nurses’ Health Study II, which enrolled much younger women with primarily premenopausal cancer found no protective effect of physical activity during either 6 or 10 years of follow-up (7, 25).

Subsequently, seven large cohort studies have been newly published or updated, contributing information on thousands of additional cases of breast cancer. Of these recent cohort studies, three studied exclusively postmenopausal women and found about a 25% to 30% reduction in the risk of breast cancer in the most compared with the least physically active groups (26-28). The remaining studies enrolled both premenopausal and postmenopausal women, and three found that a protective effect of physical activity on breast cancer was restricted to women who were either postmenopausal or at least 50 years old at enrollment (9-11). The only null study was a population-based study in Finland, which found no association of physical activity with breast cancer in any age group (29). Thus, taking into account recent reports, a reduction of postmenopausal breast cancer risk by physical activity seems quite well-established and consistent with our finding of possible effect modification by menopausal status at enrollment. Our null study contributes data on a large cohort of primarily premenopausal women to the cohort study literature.

Disparate results between the effect of physical activity on premenopausal and postmenopausal breast cancer have been seen in several population-based case-control studies using

| Table 3. RR and 95% CI of incident breast cancer among 99,504 Norwegian and Swedish women in the Women’s Lifestyle Health Cohort, by physical activity level, 1991 to 2000 |
|---------------------------------|-----------------|-----------------|-----------------|
| **Physical activity at enrollment** | **n** | **Breast cancer cases** | **Person-years** | **Age-adjusted RR** | **Multivariable RR (95% CI)** |
| None | 45 | 42,512 | 1.0 | 1.0 |
| Low | 207 | 138,699 | 1.45 | 1.35 (0.96-1.90) |
| Moderate | 576 | 441,286 | 1.27 | 1.26 (0.91-1.74) |
| High | 238 | 187,638 | 1.26 | 1.19 (0.85-1.67) |
| Vigorous | 92 | 68,536 | 1.35 | 1.24 (0.85-1.82) |
| P for trend | | | 0.88 | 0.85 |

| Physical activity at age 30 | **n** | **Breast cancer cases** | **Person-years** | **Age-adjusted RR** | **Multivariable RR (95% CI)** |
| None | 24 | 22,660 | 1.0 | 1.0 |
| Low | 122 | 104,164 | 1.07 | 1.03 (0.64-1.66) |
| Moderate | 647 | 491,779 | 1.11 | 1.16 (0.74-1.81) |
| High | 258 | 199,524 | 1.09 | 1.06 (0.67-1.68) |
| Vigorous | 104 | 74,702 | 1.17 | 1.20 (0.77-1.95) |
| P for trend | | | 0.52 | 0.60 |

| Physical activity at age 14 | **n** | **Breast cancer cases** | **Person-years** | **Age-adjusted RR** | **Multivariable RR (95% CI)** |
| None | 36 | 26,424 | 1.0 | 1.0 |
| Low | 108 | 85,110 | 0.94 | 0.93 (0.62-1.39) |
| Moderate | 506 | 404,029 | 0.91 | 0.94 (0.65-1.35) |
| High | 304 | 218,071 | 1.06 | 1.07 (0.73-1.55) |
| Vigorous | 201 | 158,050 | 1.00 | 1.05 (0.72-1.54) |
| P for trend | | | 0.21 | 0.14 |

| Competitive physical activity | **n** | **Breast cancer cases** | **Person-years** | **Age-adjusted RR** | **Multivariable RR (95% CI)** |
| None | 933 | 717,195 | 1.0 | 1.0 |
| 1-4 y | 79 | 58,119 | 0.94 | 0.93 (0.62-1.39) |
| 5+ y | 87 | 82,222 | 0.96 | 0.95 (0.75-1.21) |
| P for trend | | | 0.80 | 0.96 |

*Number of breast cancer cases do not add up because of missing values for physical activity at younger ages.

| Table 4. RR and 95% CI of incident breast cancer among 99,504 Norwegian and Swedish women in the Women’s Lifestyle Health Cohort, by changes in physical activity level, 1991 to 2000 |
|---------------------------------|-----------------|-----------------|-----------------|
| Age 14 to age 30 | **n** | **Breast cancer cases** | **Person-years** | **Crude RR** | **Multivariable RR (95% CI)** |
| Inactive—no change | 49 | 37,867 | 1.0 | 1.0 |
| Active to inactive | 96 | 88,238 | 1.00 | 0.97 (0.67-1.40) |
| Inactive to active | 95 | 73,062 | 1.06 | 1.04 (0.72-1.50) |
| Active—no change | 910 | 687,771 | 1.05 | 1.10 (0.81-1.49) |

| Age 14 to enrollment | **n** | **Breast cancer cases** | **Person-years** | **Crude RR** | **Multivariable RR (95% CI)** |
| Inactive—no change | 40 | 32,355 | 1.0 | 1.0 |
| Active to inactive | 212 | 147,137 | 1.19 | 1.31 (0.90-1.89) |
| Inactive to active | 102 | 77,067 | 1.11 | 1.20 (0.81-1.79) |
| Active—no change | 793 | 613,152 | 1.08 | 1.20 (0.85-1.71) |

| Age 30 to enrollment | **n** | **Breast cancer cases** | **Person-years** | **Crude RR** | **Multivariable RR (95% CI)** |
| Inactive—no change | 103 | 80,526 | 1.0 | 1.0 |
| Active to inactive | 149 | 99,122 | 0.95 | 0.99 (0.76-1.29) |
| Inactive to active | 40 | 42,845 | 0.66 | 0.66 (0.44-0.96) |
| Active—no change | 856 | 649,245 | 0.93 | 0.98 (0.78-1.22) |

*Number of breast cancer cases do not add up because of missing values for physical activity at younger ages.

| NOTE: Inactive refers to low or no physical activity; active refers to moderate, high, or vigorous activity.

*Data are adjusted for age at enrollment, years of education, body mass index, height, smoking status, alcohol intake, age at menarche, parity, age at first birth, number of months of breast-feeding, oral contraceptive use, family history of breast cancer, menopausal status, and country of origin.
comparable methods (30-32). Similarly, Friedenreich et al. (33, 34) found a 30% decreased risk of breast cancer among postmenopausal women who had engaged in high levels of physical activity throughout their lifetime, but no risk reduction was observed in premenopausal women. In contrast, several population-based case-control studies have found strong protective effects of physical activity among younger women (35-37).

Several lines of reasoning might explain a difference in the strength of an association between physical activity and risk of breast cancer depending on menopausal status. Rockhill et al. have hypothesized that the dissimilar results from the Nurses’ Health Study I (8) and II (7) might have resulted from a higher proportion of cancer due to highly penetrant genetic mutations in younger, premenopausal women (38). These types of tumors may be less amenable to prevention. Alternatively, adiposity might be in the causal pathway between physical activity and breast cancer. Adiposity is a risk factor for postmenopausal breast cancer and a protective factor in premenopausal breast cancer (2, 5). In postmenopausal women, adiposity increases the conversion of androgen to estrogen, in contrast to premenopausal women. In premenopausal women who do not use exogenous estrogens, this conversion in adipose tissue is the main source of circulating estrogens (39).

We acknowledge that our study has several limitations. Although sedentary behavior and physical activity levels reported by the women in our study are similar to those reported in other Scandinavian studies (2, 40), we did not directly validate our measure of self-reported physical activity. It is possible that different results might have been obtained with a more sophisticated measurement. However, several studies that showed a strong inverse relationship between physical activity and breast cancer risk used a similar instrument to measure physical activity (6, 11). Also, we found linear inverse trends with BMI and the proportion of smokers with increasing activity levels, which lends validity to the measure. Furthermore, our study found a strong negative association between physical activity and total mortality, suggesting that the measurement was sufficient to detect the association between physical activity and breast cancer. These characteristics of the cancers, including size, stage or estrogen/progesterin receptor status, as these are not included in the analysis. However, several population-based case-control studies have found a strong inverse relationship between self-reported physical activity and breast cancer risk. A prospective study of the effect of physical activity and breast cancer risk in Norway; refs. 17, 18)

In summary, we did not find evidence of a protective effect of physical activity on incident breast cancer in this cohort of relatively young, moderately active, and primarily premenopausal women. Updating of exposure and risk factor data is now under way for the entire cohort. This study, as well as further follow-up of other cohorts may resolve the present uncertainties about the effect of physical activity on breast cancer in younger women.

Acknowledgments

We thank all of the women who contributed to the study.

References


Physical Activity in Different Periods of Life and the Risk of Breast Cancer: The Norwegian-Swedish Women’s Lifestyle and Health Cohort Study


Updated version  Access the most recent version of this article at: [http://cebp.aacrjournals.org/content/14/1/27](http://cebp.aacrjournals.org/content/14/1/27)

Cited articles  This article cites 36 articles, 5 of which you can access for free at: [http://cebp.aacrjournals.org/content/14/1/27.full#ref-list-1](http://cebp.aacrjournals.org/content/14/1/27.full#ref-list-1)

Citing articles  This article has been cited by 8 HighWire-hosted articles. Access the articles at: [http://cebp.aacrjournals.org/content/14/1/27.full#related-urls](http://cebp.aacrjournals.org/content/14/1/27.full#related-urls)

E-mail alerts  Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions  To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions  To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.