Physical Activity in Relation to Mammographic Density in the Dutch Prospect-European Prospective Investigation into Cancer and Nutrition Cohort

Karijn P.M. Suijkerbuijk,[1] Fränzel J.B. Van Duijnhoven,[1] Carla H. Van Gils,[1] Paulus A.H. Van Noord,[1] Petra H.M. Peeters,[1] Christine M. Friedenreich,[2] and Evelyn M. Monninkhof[1]

[1]Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, the Netherlands and
[2]Division of Population Health and Information, Alberta Cancer Board, Calgary, Alberta, Canada

Abstract

Background: **Evidence accumulates that physical inactivity is one of the few modifiable risk factors for breast cancer. The mechanism through which physical inactivity affects breast cancer risk is not clear. The study aim was to investigate the association between physical activity and breast density because mammographic density is strongly associated with breast cancer risk.**
Methods: **We did a cross-sectional study in 620 women, of ages 49 to 68 years and participants of the Dutch Prospect-European Prospective Investigation into Cancer and Nutrition cohort. A self-administered questionnaire was used to obtain information on duration and intensity of physical activity (recreational, household, and occupational) during the year preceding study recruitment. A total activity index (inactive, moderately inactive, moderately active, and active) was estimated by combining all activity types. Percent and absolute breast density were determined on screening mammograms using a computer-aided method. Multivariate linear regression was used to examine the association between physical activity and breast density.**
Results: **Mean percent density was 35.3% [95% confidence interval (95% CI), 31.8-38.8] for the inactive category compared with 36.1% (95% CI, 33.0-39.2) for the active category. Mean absolute density values for the inactive and active category were 45.8 cm^2 (95% CI, 40.9-50.7) and 42.6 cm^2 (95% CI, 38.3-47.0), respectively. Subgroup analysis for postmenopausal women showed similar results, as did separate analyses for recreational and household activity.**
Conclusions: **The result does not support a relation between current physical activity and mammographic density in postmenopausal women.** (Cancer Epidemiol Biomarkers Prev 2006;15(3):456–60)

Introduction

Evidence on the relationship between physical activity and breast cancer is fairly consistent because the majority of studies indicate that physical activity is inversely associated with breast cancer risk with 30% to 50% risk decreases found on average. The evidence for a protective effect of physical activity on breast cancer risk has been classified as ''convincing'' (1-3). Thus far, little is known about the optimal duration, intensity, and frequency of activity needed to reduce breast cancer risk (1, 2). Furthermore, the mechanisms by which physical activity influences breast cancer risk remain unclear. Physical activity may protect against breast cancer through reduced lifetime exposure to sex steroid hormones, reduced exposure to insulin and insulin-like growth factors, and prevention of overweight and obesity (4-11).

Mammographic density is an estimate of the proportion of fibroglandular tissue in the breast. Fat is radiolucent and appears dark on a mammogram whereas epithelial tissue and stroma are radiodense and appear light. Mammographic density is related to hormonal factors. Women who are premenopausal, nulliparous, or who use hormone replacement therapy have a higher mammographic density (12, 13). A strong association has been reported between breast cancer risk and the level of breast tissue density assessed by mammography (14, 15). This association remains after adjustment for potential confounding factors, which indicates that mammographic density is an independent risk factor for the development of breast cancer. Compared with women with no visible density, women having a density of 60% to 75% had a 4- to 6-fold increase of breast cancer risk (14, 15).

Few studies have investigated the association between physical activity and breast density (16-18). Two studies found a borderline significant protection (16, 17) and one study found no association at all (18). None of the three studies assessed physical activity in detail.

The purpose of this study is to examine the relation between several types of physical activity (recreational, occupational, household, and total) and mammographic density in a cohort of mainly postmenopausal women to elucidate mechanisms by which physical inactivity increases breast cancer risk.

Materials and Methods

A cross-sectional study was conducted within the Prospect-European Prospective Investigation into Cancer and Nutrition (EPIC) cohort, which is one of the two Dutch cohorts participating in the EPIC study (19). Details of this cohort have been published elsewhere (20). In brief, healthy women living in Utrecht (the Netherlands) and surroundings were recruited through a population-based breast cancer screening program

Received 8/2/05; revised 12/28/05; accepted 1/19/06.
Grant support: Dutch Cancer Society grant UU 2002-2716.
The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked advertisement in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.
Requests for reprints: E.M. Monninkhof, Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, the Netherlands.
E-mail: E.Monninkhof@umcutrecht.nl

doi:10.1158/1055-9965.EPI-05-0569

[3] F.J.B. van Duijnhoven et al. Genetic susceptibility to the effects of hormone therapy on mammographic density. Cancer Epidemiol Biomarkers Prev, to appear.

between 1993 and 1997. For the present analysis, we selected 620 women from the Prospect-EPIC cohort. These women never used postmenopausal hormone therapy and formed the reference group in a follow-up study on the effect of hormone therapy use on mammographic density.[3] Women participating in this study were of ages 49 to 68 years at recruitment. Exclusion criteria were current use of oral contraceptives and breast cancer diagnosis before or within 2 years after mammography.

Prospect-EPIC participants completed self-administered questionnaires about demographic characteristics, chronic disease, medical history, reproductive history, smoking and drinking habits, and physical activity, as well as a food-frequency questionnaire. All information was collected at study recruitment. Anthropometric measures (i.e., height, weight, and waist and hip circumference) used for this analysis were gathered by physical examination (20).

Physical Activity Measurement. Information on physical activity was acquired through a self-administered questionnaire (21). Participants were asked whether or not they had a job and what the intensity of physical activity during work was. Occupational activity was classified as sedentary, standing, manual, or heavy manual. For nonoccupational activities (housework, walking, cycling, gardening, do-it-yourself, and sports), subjects were asked to estimate the number of hours spent on these activities during a normal week in summer and winter separately. A separate question was posted about the number of flights of stairs climbed per day.

To make the collected data more accessible and suitable for analysis, we first computed a total physical activity index. A group of EPIC researchers working on physical activity developed and tested this physical activity index and recommended its use. We computed the mean hours spent on each recreational activity (walking, cycling, and sporting) in summer and winter. We used cutoff points to correct for unreasonable high values. Limits were, depending on kind of activity, between 15 and 59 hours a week. To compute the total energy expenditure in metabolic equivalent (MET) hours, we multiplied the number of hours spent on each activity by an activity-specific intensity code, as recommended by Ainsworth et al. (22). One MET-hour is the equivalent of the energy expenditure of 1 hour in rest. The intensity code for cycling is 6 MET whereas the numbers of hours spent on walking were multiplied by 3 MET. The individual recreational activities were combined to estimate total recreational activity.

Then, we used the same approach to compute household activity as the sum of activities including housework, gardening, do-it-yourself work, and number of stairs climbed. The estimation of energy spent on climbing stairs per week was done as follows: 20 [steps/flight] / 72 [steps a minute] $\times$ 60 $\times$ number of flights a day $\times$ 8 MET $\times$ 7 [days a week].

We summed the recreational and household activity to combined recreational and household activity. This value was divided into quartiles based on the distribution of our study population and cross-classified with the occupational activity categories (see Table 1). The result is a score for total physical activity consisting of four categories, inactive, moderately inactive, moderately active, and active, composed as recommended by the above-mentioned EPIC physical activity research group.

Mammographic Density Analysis. Mammographic density of the left breast was assessed using the mediolateral oblique view, the routine view for breast cancer screening in the Netherlands. It has been observed that the proportions of mammographic density on craniocaudal views and mediolateral oblique views and on left and right views are very strongly correlated and that representative information on mammographic density is provided in a single view (23). The mammogram taken closest to the date of filling out the questionnaire was analyzed. After digitizing the films using a laser film scanner (Lumiscan 50, Lumisys), mammographic density was quantified using a computer-assisted method based on gray levels (24). This computer-assisted method to determine mammographic density has been shown to be very reliable (16, 17, 24). For each image, the reader first sets a threshold to determine the outside edge of the breast. Another threshold is set to determine the area of dense tissue within the breast, which is the lightest tissue visible. The computer then determines the number of pixels within the dense area and within the total breast and calculates the percentage of dense tissue. All images were read by one observer (F.v-D.) in sets of 70 images composed of randomly ordered films. To assess the reproducibility of the reader working with the computer-assisted method, a library set of 70 images was made, which consisted of randomly chosen films that were not included in our study. This library set was read before the first set, after the last set, and at three time points between sets, which were blinded for the reader. In this study, an average intraclass correlation coefficient of 0.87 (range, 0.82-0.90) for absolute density and 0.93 (range 0.91-0.95) for percent density was reached between repeated readings.

Percent density is currently the most frequently used measure of mammographic density. Because software programs exist that assess continuous levels of density, absolute density can also be measured. Because the dense area is regarded to contain the target tissue for breast cancer, the absolute amount of dense tissue, instead of relative amount, may be more relevant to study (25). We therefore present results for both relative and absolute measures of breast density.

Screening mammograms were available for 618 of 620 women. Two persons were left out of analysis because of missing values on occupational and recreational activity variables. Analysis was subsequently done on 616 participants.

Statistical Analysis. Linear regression was used to examine the effect of total physical activity adjusted for the effect of potential confounding factors. The following factors, which might be associated with both physical activity and mammographic density, were considered for confounding: age, body mass index (BMI), waist-to-hip ratio, smoking (pack years), alcohol intake (units per day), energy intake (kcal), age at menarche, number of live births, age at first delivery (all continuous), education (primary, technical/professional, secondary school, university), previous oral contraceptive use

Table 1. Definition of activity levels for combined total physical activity index according to reported occupational, recreational, and household activity

Occupational activity	Low (<87.07 MET-h/wk)	Combined recreational and household activity		
		Medium (87.07-118.30 MET-h/wk)	High (118.31-158.35 MET-h/wk)	Very high (>158.35 MET-h/wk)
Sedentary	Inactive	Inactive	Moderately inactive	Moderately active
Standing	Moderately inactive	Moderately inactive	Moderately active	Active
Heavy manual	Moderately active	Moderately active	Active	Active
Unemployed	Moderately inactive	Moderately inactive	Moderately active	Moderately active

Table 2. Baseline characteristics of the Dutch Prospect-EPIC cohort

	Inactive, % (*n*)	Moderately inactive, % (*n*)	Moderately inactive, % (*n*)	Active, % (*n*)	Group total, % (*n*)
Age (y), mean (SD)	52.9 (3.2)	55.3 (4.3)	55.3 (4.1)	54.0 (3.4)	54.8 (4.0)
Menopausal status					
Premenopausal	32% (24)	20% (37)	21% (44)	28% (25)	23% (130)
Postmenopausal <45	17% (17)	32% (31)	39% (38)	12% (12)	18% (98)
Postmenopausal 45-50	22% (16)	26% (48)	26% (55)	20% (18)	25% (137)
Postmenopausal >50	23% (17)	37% (67)	35% (75)	39% (35)	35% (194)
Age menarche (y)					
<12	10% (8)	7% (13)	9% (20)	7% (7)	8% (48)
12	30% (23)	22% (43)	18% (41)	23% (24)	22% (131)
13	30% (23)	31% (60)	29% (67)	24% (25)	29% (175)
>13	30% (23)	41% (79)	44% (102)	46% (48)	42% (252)
Age first delivery (y)					
<25	42% (30)	48% (83)	48% (106)	42% (42)	46% (261)
25-29	54% (38)	43% (75)	41% (90)	49% (48)	44% (251)
≥30	4% (3)	9% (16)	11% (25)	9% (9)	9% (53)
No. live births					
0	11% (9)	12% (24)	6% (13)	5% (5)	8% (51)
1-2	60% (48)	38% (75)	46% (107)	50% (52)	46% (282)
>2	29% (23)	50% (99)	49% (114)	45% (47)	46% (283)
BMI (kg/m^2)					
<25	48% (38)	49% (97)	45% (104)	35% (36)	45% (275)
25-30	41% (32)	37% (73)	43% (100)	48% (50)	42% (255)
>30	11% (9)	14% (28)	12% (29)	17% (18)	14% (84)
Waist-to-hip ratio					
<0.75	44% (35)	26% (52)	25% (59)	28% (29)	29% (175)
0.75-0.8	32% (25)	43% (86)	41% (96)	29% (30)	39% (237)
>0.8	24% (19)	30% (60)	34% (79)	43% (45)	33% (203)
Pill use ever					
Yes	81% (65)	69% (136)	71% (165)	70% (73)	71% (439)
No	19% (15)	31% (62)	30% (69)	30% (31)	29% (177)
Smoking (pack years)					
0	43% (34)	44% (84)	56% (127)	49% (48)	49% (293)
0-5	17% (13)	22% (42)	15% (33)	23% (23)	19% (111)
5-10	14% (11)	13% (25)	9% (20)	14% (14)	12% (70)
>10	27% (21)	21% (40)	21% (48)	14% (14)	21% (123)
Alcohol (units/wk)					
<1	25% (20)	32% (63)	33% (76)	37% (38)	32% (197)
1-5	24% (19)	24% (48)	32% (74)	31% (32)	28% (173)
5-10	19% (15)	13% (26)	11% (25)	14% (14)	13% (80)
>10	33% (26)	31% (60)	25% (58)	19% (20)	27% (164)
Education completed					
Primary school	4% (3)	14% (27)	15% (34)	14% (14)	13% (78)
Technical/professional	18% (14)	33% (64)	31% (73)	45% (47)	32% (198)
Secondary school	51% (41)	27% (53)	35.6 (83)	19% (20)	32% (197)
University degree	28% (22)	27% (53)	19% (43)	22% (23)	23% (141)
Total	13% (80)	32% (198)	38% (234)	17% (104)	100% (616)

(yes/no), and menopausal status (premenopausal, postmenopausal <45, postmenopausal 45-50, postmenopausal >50 years). Postmenopausal was defined as at least 12 consecutive months of amenorrhea.

Outcome measures were percent and absolute mammographic density. First, we assessed the crude relation between total physical activity and density. Second, we added all potential confounders and removed them singly through backwards elimination to evaluate which factors were related to density as well as to physical activity. A factor was considered as a relevant confounder if it changed the regression coefficient by >10%.

To compute means of percent and absolute density values for all four categories of total physical activity, we created four representative women in the database: one inactive, the second moderately inactive, the third moderately active, and a fourth active one. We used linear regression to estimate the crude mean values of percent and absolute density with their corresponding confidence limits. Subsequently, we estimated the adjusted means and their confidence intervals for the different categories of activity by assigning mean values for relevant confounders to each representative.

For statistical analyses, we used SPSS version 12.0.1.

Results

The mean age of participants was 54.8 (SD, 4.0) years and 78% of the women were postmenopausal. Baseline characteristics of the study population and the distribution of the physical activity indices are shown in Table 2. The smallest percentage (13%) of the women were classified as inactive, 32% were moderately inactive, 38% were moderately active, and 17% were active. In our population, walking accounted for ~18%, cycling for 20%, and housework for 45% of total nonoccupational energy expenditure (data not shown).

In our data, we confirmed the expected relationships between mammographic density and hormone-related factors. Women who were younger, nulliparous, or premenopausal had a high percent and absolute mammographic density. BMI and waist-to-hip ratio were only inversely associated with percent density, not with absolute density (data not shown).

Mean percent and absolute density values for the four different categories of physical activity are shown in Table 3. Crude percent density means were 38.5% [95% confidence interval (95% CI), 34.9-42.0] for the inactive, 36.0% (95% CI, 33.7-38.2) for the moderately inactive, 34.6% (95% CI, 32.6-36.7) for the moderately active, and 35.0% (95% CI, 31.9-38.1) for the

Table 3. Mean mammographic density according to physical activity (all women)

	n	Crude mean	95% CI	*β*	*P*	Adjusted mean	95% CI	*β*	*P*
Percent density (%)									
Total physical activity									
Inactive	80	38.5	34.9-42.0	Reference	Reference	35.3*	31.8-38.8	Reference	Reference
Moderately inactive	198	36.0	33.7-38.2	−2.51	0.24	36.5*	34.2-38.7	1.17	0.59
Moderately active	234	34.6	32.6-36.7	−3.83	0.07	34.1*	32.1-36.1	−1.22	0.56
Active	104	35.0	31.9-38.1	−3.49	0.15	36.1*	33.0-39.2	0.75	0.76
Absolute density (cm^2)									
Total physical activity									
Inactive	80	47.0	42.6-51.4	Reference	Reference	45.8 †	40.9-50.7	Reference	Reference
Moderately inactive	198	44.4	41.6-47.3	−2.56	0.34	44.7 †	41.5-47.8	−1.14	0.70
Moderately active	234	43.6	41.0-46.2	−3.42	0.19	43.0 †	40.2-45.8	−2.80	0.33
Active	104	43.2	39.4-47.1	−3.76	0.21	42.6 †	38.3-47.0	−3.18	0.34

*Adjusted for BMI, waist-to-hip ratio, smoking, education, menopausal status, parity, and age.
†Adjusted for smoking, menopausal status, parity, and age.

active. Crude means of absolute density for the inactive, moderately inactive, moderately active, and active were 47.0 cm^2 (95% CI, 42.6-51.4), 44.4 cm^2 (95% CI, 41.6-47.3), 43.6 cm^2 (95% CI, 41.0-46.2), and 43.2 cm^2 (95% CI, 39.4-47.1), respectively (see Table 3).

In assessing the relation between physical activity and percent density, age, education, BMI, waist-to-hip ratio, menopausal status, parity, and smoking were identified as confounding factors and included in the multivariate linear regression model. The relation between physical activity and absolute density was confounded by age, menopausal status, parity, and smoking.

Mean percent density adjusted for the above-mentioned confounding factors was 35.3% (95% CI, 31.8-38.8) for the inactive, 36.5% (95% CI, 34.2-38.7) for the moderately inactive, 34.1% (95% CI, 32.1-36.1) for the moderately active, and 36.1% (95% CI, 33.0-39.2) for the active (see Table 3). The adjusted means of absolute density values for the inactive, moderately inactive, moderately active, and active category were 45.8 cm^2 (95% CI, 40.9-50.7), 44.7 cm^2 (95% CI, 41.5-47.8), 43.0 cm^2 (95% CI, 40.2-45.8), and 42.6 cm^2 (95% CI, 38.3-47.0), respectively. Subgroup analysis for postmenopausal women (Table 4) showed similar results.

Finally, subgroup analysis for frequently done activities (such as cycling and walking) and recreational activity and household activity, separately, did not show an association with either percent or absolute breast density (see Table 5).

Discussion

Overall, we did not find an association between current physical activity and mammographic density in this group of mostly postmenopausal women. A slight trend was observed for the effect of physical activity on absolute density. The effect, however, was very small and was not reflected in the percent density measurements.

Comparable results were found by Vachon et al. (18). The authors investigated the effect of potential breast cancer risk factors on percent mammographic density in a breast cancer proband cohort. Information on usual physical activity of 1,900 mostly postmenopausal women (age, 40-93 years) was collected through telephone interviews. Physical activity was classified as low, moderate, or high based on reported frequencies of lifetime vigorous and moderate activities. No association was found between physical activity and percent density.

Lopez et al. (17) investigated the association between inactivity and percent breast density among 294 Hispanic women over the age of 40. Participants were divided by interview-based data into three categories of number of hours of inactivity a day (watching television, reading, knitting or using a computer). Percent density was marginally significantly higher for women that had at least 3.5 hours of physical inactivity (mean percent density, 20.1%) compared with women that reported to have 0 to 1 hour of physical inactivity each day (mean percent density, 17.3%). The results of this study are hardly comparable to our study because physical inactivity measures are used. Furthermore, percent density means reported are low whereas the described methods of density measurement were comparable to ours.

Gram et al. (16) studied physical activity and mammographic patterns in a population of 2,720 Norwegian women, ages 40 to 56 years. Density was described according to the categorical Tabar's classification (26). Concise information on occupational, leisure, and vigorous physical activity during the preceding year was collected at two different points in 7 years through a two- and five-question-containing questionnaire. Women having >2 hours of physical activity a week less often showed high-risk mammographical patterns (odds ratio, 0.8; 95% CI, 0.6-1.1).

Strength of our study is that we used continuous measures for both percent density and absolute density as outcome measures whereas in previous studies only percent density or semiquantitative measures of density were used. Quantitative measures such as percent and absolute breast density seem to

Table 4. Mean mammographic density according to physical activity in postmenopausal women

	n	Mean percent density (%)*	95% CI	*β*	*P*	Mean absolute density (cm^2) †	95% CI	*β*	*P*
Total physical activity									
Inactive	50	33.4	29.3-37.5	Reference	Reference	44.7	38.9-50.4	Reference	Reference
Moderately inactive	146	35.2	32.7-37.8	1.80	0.47	43.8	40.2-47.5	−0.87	0.81
Moderately active	168	33.3	31.0-35.6	-0.13	0.96	42.6	39.4-45.8	−2.03	0.55
Active	66	35.3	31.8-38.9	1.91	0.49	41.7	36.7-46.8	−2.96	0.45

*Adjusted for BMI, waist-to-hip ratio, smoking, education, parity, and age.
† Adjusted for smoking, parity, and age.

Table 5. Mean mammographic density according to different physical activities

	n	Mean percent density (%)*	95% CI	*β*	*P*	Mean absolute density (cm^2)†	95% CI	*β*	*P*
Cycling (MET-h/wk)									
<10	163	35.5	33.0-38.0	Reference	Reference	44.6	41.1-48.1	Reference	Reference
10-20	158	35.4	32.9-37.9	−0.11	0.95	44.3	40.9-47.8	−0.27	0.91
20-36	136	34.7	32.0-37.3	−0.83	0.65	42.7	39.0-46.4	−1.91	0.46
>36	159	35.7	33.2-38.1	0.15	0.93	43.7	40.2-47.1	−0.94	0.71
Walking (MET-h/wk)									
<7	158	34.8	32.4-37.3	Reference	Reference	43.8	40.4-47.3	Reference	Reference
7-15	149	37.4	34.9-39.8	2.53	0.15	44.1	40.6-47.6	0.26	0.92
15-30	148	33.8	31.2-36.4	−1.05	0.57	43.2	39.5-46.9	−0.65	0.80
>30	161	35.1	32.6-37.6	0.28	0.88	44.2	40.8-47.7	0.41	0.87
Total recreational activity‡									
<30	146	35.8	33.2-38.5	Reference	Reference	45.3	41.6-49.0	Reference	Reference
30-47	163	35.7	33.3-38.1	−0.09	0.96	44.4	41.1-47.8	−0.84	0.74
47-75	153	34.5	32.0-37.0	−1.34	0.46	42.5	39.0-46.0	−2.78	0.28
>75	154	35.3	32.7-37.8	−0.56	0.76	43.3	39.8-46.8	−1.97	0.45
Total household activity§									
<40	154	34.0	31.4-36.5	Reference	Reference	43.1	39.6-46.7	Reference	Reference
40-64	158	37.1	34.6-39.6	3.10	0.08	43.2	39.7-46.6	0.03	0.99
64-92	152	36.8	34.3-39.3	2.82	0.12	47.0	43.5-50.5	3.87	0.13
>92	152	33.3	30.8-35.8	−0.68	0.71	42.2	38.7-45.7	−0.93	0.72

*Adjusted for BMI, waist-to-hip ratio, smoking, education, menopausal status, parity, and age.
†Adjusted for smoking, menopausal status, parity, and age.
‡Total recreational activity: cycling, walking, and sporting.
§Total household activity: housework, gardening, do-it-yourself work and number of stairs climbed.

be stronger risk factors for breast cancer development than semiquantitative measures (27). Furthermore, we used a physical activity index that comprised information on multiple areas of physical activity.

Some methodologic aspects should be mentioned. Although we obtained information of physical activity of all sources, the fact that questionnaires were self-administered and measured only activity at enrollment into the study might have caused misclassification of physical activity. One main limitation with the EPIC physical activity data is the lack of information on the duration and frequency of occupational activity. In addition, it could be important to have information on all types of activity over lifetime because activity at different time periods may influence mammographic density later in life. Despite these limitations, Pols et al. (21) found a satisfactory reproducibility for the EPIC physical activity questionnaire and concluded that it is suitable for ranking subjects in the EPIC study. Because we wanted to differentiate between different categories of activity and were less interested in absolute physical activity values, we believed that the EPIC questionnaire provides adequate information for this purpose.

As mentioned before, little is known about the optimal intensity of physical activity needed to reduce breast cancer risk. It is possible that only vigorous activity reduces breast cancer risk. In this study, very limited information on vigorous activity was available. Furthermore, as this analysis includes mostly postmenopausal women, conclusions about the effect of physical activity on mammographic density at a younger age cannot be drawn.

In our study, we found unexpected positive correlations between physical activity and waist-to-hip ratio and BMI (see Table 2). There are a few possible explanations for these findings. First, physical activity might prevent age-related weight loss and sarcopenia in elderly women. Elderly women with a relatively low physical activity level usually have a lower energy intake compared with active elderly women, which might result in a lower body weight and fat-free mass (28). Second, because current physical activity is measured, it might be the case that obese women have raised their activity level to lose weight. Additionally, as mentioned before, some misclassification of physical activity levels cannot be excluded.

In summary, we found no association between current physical activity and mammographic density in this mainly postmenopausal population. Future studies with detailed information on physical activity over a longer period are needed to confirm our finding that the effect of physical activity on breast cancer risk is not mediated through an effect on mammographic density.

Acknowledgments

We thank Dr. Norman Boyd for the training in mammographic density assessment and Prof. Martin Yaffe and his department for the technical support of the computer-assisted software to determine mammographic density; Stichting Preventicon and the ''Vereniging van Vriendinnen van het DOM project'' for making the mammograms from all participants available; Bernard Slotboom for assisting in selecting the study populations; Joke Metselaar-van den Bos, Bert Rodenburg, and Jelmer Hoefakker for assisting in identifying and collecting the mammograms; and Jantine Schuit for her helpful advice.

References

1. Gammon MD, John EM, Britton JA. Recreational and occupational physical activities and risk of breast cancer. J Natl Cancer Inst 1998;90:100–17.
2. Hardman AE. Physical activity and cancer risk. Proc Nutr Soc 2001;60: 107–13.
3. Friedenreich CM. Physical activity and cancer prevention: from observational to intervention research. Cancer Epidemiol Biomarkers Prev 2001;10:287–301.
4. Bergstrom A, Pisani P, Tenet V, Wolk A, Adami HO. Overweight as an avoidable cause of cancer in Europe. Int J Cancer 2001;91:421–30.
5. Irwin ML, Yasui Y, Ulrich CM, et al. Effect of exercise on total and intra-abdominal body fat in postmenopausal women: a randomized controlled trial. JAMA 2003;289:323–30.
6. Key TJ, Appleby PN, Reeves GK, et al. Body mass index, serum sex hormones, and breast cancer risk in postmenopausal women. J Natl Cancer Inst 2003;95:1218–26.
7. McTiernan A, Tworoger SS, Ulrich CM, et al. Effect of exercise on serum estrogens in postmenopausal women: a 12-month randomized clinical trial. Cancer Res 2004;64:2923–8.
8. Muti P, Quattrin T, Grant BJ, et al. Fasting glucose is a risk factor for breast cancer: a prospective study. Cancer Epidemiol Biomarkers Prev 2002;11:1361–8.
9. Shi R, Yu H, McLarty J, Glass J. IGF-I and breast cancer: a meta-analysis. Int J Cancer 2004;111:418–23.
10. Weight control and physical activity. Lyon: IARC Press; 2002.
11. Frisch RE, Wyshak G, Vincent L. Delayed menarche and amenorrhea in ballet dancers. N Engl J Med 1980;303:17–9.

12. Boyd NF, Lockwood GA, Byng JW, Tritchler DL, Yaffe MJ. Mammographic densities and breast cancer risk. Cancer Epidemiol Biomarkers Prev 1998;7:1133–44.
13. Warren R. Hormones and mammographic breast density. Maturitas 2004;49:67–78.
14. Boyd NF, Byng JW, Jong RA, et al. Quantitative classification of mammographic densities and breast cancer risk: results from the Canadian National Breast Screening Study. J Natl Cancer Inst 1995;87:670–5.
15. Byrne C, Schairer C, Wolfe J, et al. Mammographic features and breast cancer risk: effects with time, age, and menopause status. J Natl Cancer Inst 1995;87:1622–9.
16. Gram IT, Funkhouser E, Tabar L. Moderate physical activity in relation to mammographic patterns. Cancer Epidemiol Biomarkers Prev 1999;8:117–22.
17. Lopez P, Van Horn L, Colangelo LA, Wolfman JA, Hendrick RE, Gapstur SM. Physical inactivity and percent breast density among Hispanic women. Int J Cancer 2003;107:1012–6.
18. Vachon CM, Kuni CC, Anderson K, Anderson VE, Sellers TA. Association of mammographically defined percent breast density with epidemiologic risk factors for breast cancer (United States). Cancer Causes Control 2000;11:653–62.
19. Riboli E. Nutrition and cancer: background and rationale of the European Prospective Investigation into Cancer and Nutrition (EPIC). Ann Oncol 1992;3:783–91.
20. Boker LK, van Noord PA, van der Schouw YT, et al. Prospect-EPIC Utrecht: study design and characteristics of the cohort population. European Prospective Investigation into Cancer and Nutrition. Eur J Epidemiol 2001;17:1047–53.
21. Pols MA, Peeters PH, Ocke MC, Slimani N, Bueno-de-Mesquita HB, Collette HJ. Estimation of reproducibility and relative validity of the questions included in the EPIC Physical Activity Questionnaire. Int J Epidemiol 1997;26 Suppl 1:S181–9.
22. Ainsworth BE, Haskell WL, Whitt MC, et al. Compendium of physical activities: an update of activity codes and MET intensities. Med Sci Sports Exerc 2000;32:S498–504.
23. Byng JW, Boyd NF, Little L, et al. Symmetry of projection in the quantitative analysis of mammographic images. Eur J Cancer Prev 1996;5:319–27.
24. Byng JW, Boyd NF, Fishell E, Jong RA, Yaffe MJ. The quantitative analysis of mammographic densities. Phys Med Biol 1994;39:1629–38.
25. Albanes D, Winick M. Are cell number and cell proliferation risk factors for cancer? J Natl Cancer Inst 1988;80:772–4.
26. Gram IT, Funkhouser E, Tabar L. The Tabar classification of mammographic parenchymal patterns. Eur J Radiol 1997;24:131–6.
27. Brisson J, Diorio C, Masse B. Wolfe's parenchymal pattern and percentage of the breast with mammographic densities: redundant or complementary classifications? Cancer Epidemiol Biomarkers Prev 2003;12:728–32.
28. Ekelund U, Brage S, Franks PW, et al. Physical activity energy expenditure predicts changes in body composition in middle-aged healthy whites: effect modification by age. Am J Clin Nutr 2005;81:964–9.