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Report

Body fat distribution in relation to breast cancer in women participating in the DOM-project

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Summary

The association between body fat distribution and breast cancer risk was studied in 5923 pre- and 3568 postmenopausal women, participating in a breast cancer screening project (the DOM-project in Utrecht, the Netherlands). Cases were fifty six premenopausal women and thirty eight postmenopausal women with breast cancer detected at screening or afterwards. Controls were women participating in the breast cancer screening project without breast cancer. Waist- and hip circumferences, height and weight were measured at screening, before diagnosis of breast cancer.

In postmenopausal women the estimated relative risk of women in the upper tertile of waist/hip ratio compared with women in the lower tertile was 1.89 (95% CI 0.80–4.48), (test for trend p = 0.11). The estimated relative risk of women in the upper tertile of waist circumference compared with women in the lower tertile was 2.86 (95% CI I 1.12–7.32), (test for trend p = 0.08). The association between waist circumference and breast cancer was stronger than the association between any of the other anthropometric variables and breast cancer.

In premenopausal women the association between fat distribution and breast cancer was equivocal.

Introduction

It was noted as early as 1960, that in the study of the relationship between obesity and breast cancer, it is important to discriminate between premenopausal- and postmenopausal breast cancer [1]. Only the postmenopausal type of carcinoma was reported to be associated with obesity. Since 1960 many studies observed modest positive relationships between obesity and breast cancer in postmenopausal women, as reviewed by Osler [2]. In more recent studies this positive association was confirmed [3–5], although in two recent prospective studies no increased risk for breast cancer in more obese postmenopausal women was observed [6, 7]. Most of the studies in premenopausal women report inverse relationships, as reviewed by Osler [2] and confirmed in more recent studies [3, 4, 6, 8], although other studies reported the absence of a relationship as reviewed by Osler [2] and confirmed in a recent study [5].

Since 1988 the pattern of body fat distribution has been studied as a potential risk factor for breast cancer [9]. Body fat distribution has been related to a number of other chronic illnesses, independently from obesity [10].

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An abdominal fat distribution as measured by waist/hip ratio was found to be positively related to breast cancer in postmenopausal women in two studies [11, 13], but no relationship was found in two other studies [14, 15]. In still another study women in the upper quartile of a central adiposity ratio (sum of truncal skinfolds divided by sum of extremity skinfolds) were found to be at increased risk for breast cancer [7]. Sellers and colleagues [12], using the same cohort as Folsom and colleagues [11], reported that the positive association between waist/hip ratio and breast cancer was limited to women with a family history of breast cancer. In the studies that analysed premenopausal women separately, no significant relationships between abdominal fat distribution and breast cancer were found [13–15].

In a recent study by Petrek *et al.* an inverse, although non significant, relationship between abdominal fat distribution and breast cancer in postmenopausal women was found, and no relationship was found in premenopausal women [15]. In the study by Petrek *et al.*, the control group consisted of women with benign breast disease [15]. Although the authors present evidence that their control group is valid, it cannot be excluded that such a control group has introduced bias. The authors suggest that further studies are needed and should include a more diverse sample of American women.

We here present the results of a Dutch population-based case-control study in which measurement of body fat distribution was performed before diagnosis of breast cancer. Results are presented for pre- and postmenopausal women separately.

Subjects and methods

The study subjects were 9491 women aged 40–73 years attending a breast cancer screening project, the DOM-project in Utrecht, the Netherlands [16], in the period 1984 to 1986. This population has been previously described with respect to reproductive characteristics, smoking behaviour, and anthropometric characteristics [17].

Premenopausal (n = 5923) and postmenopausal women (n = 3568) were analysed separately. Women were classified as postmenopausal if they reported that their menstruations had stopped spontaneously more than 12 months before. Women who had undergone hysterectomy or ovariectomy and women with unknown menopausal status were excluded from the analyses. The mean age of the premenopausal women was 44.0 (range 40–55) years and the mean age of the postmenopausal women was 57.8 (range 40–73) years. Cases were 56 premenopausal women and 38 postmenopausal women with breast cancer detected at screening (14 pre- and 16 postmenopausal women) or during the period of follow-up to January 1st 1990 (42 pre- and 22 postmenopausal women). Follow-up of the cohort was performed by our division of registration, follow-up, and evaluation. Follow-up was estimated to be 95% complete. Lobular carcinomas *in situ* were not included. Anthropometric measurements of these women were performed at their visit for breast cancer screening by trained assistants from 1984 through 1986. Almost 80% of the postmenopausal women had been screened once or more times before 1984, the year in which measurement of waist- and hip circumference was started. Of the premenopausal women 97% were screened for the first time in the period 1984–1986. Body weight was measured to the nearest 0.1 kg. Body height was measured to the nearest 0.1 cm. Quetelet's index, calculated as weight divided by height squared (kg/m^2), was used as an indicator of body fatness. Waist girth was measured to the nearest 0.5 cm at the minimum circumference. Hip circumference was measured to the nearest 0.5 cm at the widest point of the hip area. During measurement of weight, height, waist circumference, and hip circumference, the women were standing and not wearing shoes; the upper part of the body was undressed.

Statistical methods

Statistical analyses were performed using SPSS release 4.1. Multiple logistic regression was used in order to determine age adjusted odds ratios (OR) for tertiles of height, weight, waist, hip, Quetelet's index, and waist/hip ratio. The lowest tertiles were used as reference categories. Tertiles were used in order to be able to compare the odds ratios of the various anthropometric variables and to detect a possible trend. Quartiles were not used because of small numbers. Adjustments for Quetelet's index were not made because of multicollinearity. Interaction between age and any of the anthropometric variables was tested by means of the Likelihood ratio test statistic and the Wald test for the interaction term in a model with continuous variables. Tests for trend were performed by testing the significance of the variables when entered in a model as continuous variables. Significance levels are two-sided.

Results

In premenopausal women there was significant interaction between age and waist, age and Quetelet's index, and age and waist/hip ratio. In Table 1, the mean anthropometric values and the standard deviations are described for cases and controls in premenopausal women stratified by age. The anthropometric variables were not significantly different between cases and controls aged less than 45 years. The median values for the controls for age, waist, hip, and waist/hip ratio were 42, 74.0, 98.9 and 0.75. Among premenopausal women aged 45 years or more, cases had a significant lower waist- and hip circumference as well as a lower waist/hip ratio and a lower Quetelet's index. The median values for the controls for age, waist, hip and waist/hip ratio were 48, 76.0, 101.0, and 0.76.

Table 1. Anthropometric measurements for premenopausal cases and controls stratified by age

Aged less than 45 years

Variable	Controls (n = 3815) Mean ± s.d.	Cases (n = 30) Mean ± s.d.
Age	41.7 ± 1.2	42.1 ± 1.3
Height	1.66 ± 0.06	1.65 ± 0.07
Weight	66.6 ± 11.0	66.8 ± 11.3
Waist	75.4 ± 9.3	76.6 ± 10.2
Hip	99.4 ± 8.5	98.6 ± 9.3
Quetelet's index	24.3 ± 3.9	24.4 ± 3.8
Waist/hip ratio	0.76 ± 0.06	0.78 ± 0.08

Aged 45 years or more

Variable	Controls (n = 2052) Mean ± s.d.	Cases (n = 26) Mean ± s.d.
Age	48.2 ± 2.9	48.3 ± 3.0
Height	1.66 ± 0.06	1.67 ± 0.08
Weight	68.9 ± 10.7	66.6 ± 8.1
Waist	77.9 ± 9.2	72.9 ± 5.9*
Hip	101.7 ± 8.2	98.3 ± 5.8*
Quetelet's index	25.1 ± 3.7	23.8 ± 2.7*
Waist/hip ratio	0.77 ± 0.06	0.74 ± 0.04*

* Significant by t test at p = 0.05.

In Table 2, the mean anthropometric values and standard deviations are described for postmenopausal women. Cases had on average a larger waist circumference than controls. Waist/hip ratios were larger in cases than controls at a significance level of $p < 0.10$. The median values for the controls for age, waist, hip, and waist/hip ratio were 58, 80.0, 102.2, and 0.78. We calculated age adjusted odds ratios for premenopausal women aged less than 45 years and premenopausal women aged 45 years or more separately as well. In the older premenopausal women, waist/hip ratio and waist circumference were negatively associated with breast cancer risk, whereas in the younger premenopausal women waist/hip ratio was positively and waist circumference was (nonsignificantly) positively associated with breast cancer risk. Quetelet's index was (nonsignificantly) negatively associated with breast cancer in the older premenopausal women and not associated with breast cancer risk in the younger premenopausal women. These results are not presented in a table because in our opinion not too much attention should be paid to them as the results are difficult to interpret and probably due to small numbers.

Table 2. Anthropometric measurements for postmenopausal cases and controls

Variable	Controls (n = 3530) Mean ± s.d.	Cases (n = 38) Mean ± s.d.
Age	57.8 ± 7.4	59.5 ± 7.2
Height	1.64 ± 0.06	1.65 ± 0.06
Weight	69.4 ± 11.0	70.9 ± 8.2
Waist	80.6 ± 9.3	83.6 ± 7.3*
Hip	103.1 ± 8.3	104.9 ± 8.7
Quetelet's index	25.9 ± 3.9	26.2 ± 3.0
Waist/hip ratio	0.78 ± 0.06	0.80 ± 0.06#

* Significant by t test at p = 0.05.
# Significant by t test at p = 0.10.

Table 3. Age adjusted odds ratios and 95% confidence intervals for breast cancer in tertiles of height, weight, hip, Quetelet's index, and waist/hip ratio in 3568 postmenopausal women

Variable	Odds ratio	(95% CI)	#
Height			
< 1.61	1.00	*	0.18
1.61–1.659	1.37	0.59 to 3.14	
≥ 1.66	1.51	0.69 to 3.42	
Weight			
< 64.0	1.00	*	0.42
64.0–72.99	1.49	0.65 to 3.43	
≥ 73.0	1.45	0.63 to 3.36	
Waist			
< 76.0	1.00	*	0.08
76.0–83.89	1.92	0.72 to 5.12	
≥ 83.9	2.86	1.12 to 7.32	
Hip			
< 99.3	1.00	*	0.21
99.3–105.99	1.17	0.50 to 2.71	
≥ 106.0	1.51	0.68 to 3.36	
Quetelet's index			
< 24.1	1.00	*	0.82
24.1–26.99	1.57	0.68 to 3.63	
≥ 27.0	1.45	0.62 to 3.38	
Waist/hip ratio			
< 0.76	1.00	*	0.11
0.76–0.799	1.49	0.61 to 3.64	
≥ 0.80	1.89	0.80 to 4.48	

test for trend by significance of the continuous variable.
* reference group.

Table 3 shows age-adjusted odds ratios and 95% confidence intervals for breast cancer in tertiles of height, weight, waist, hip, Quetelet's index, and waist/hip ratio for postmenopausal women. Women in the upper tertile of waist compared to women in the lower tertile had an odds ratio of 2.86 (95% CI 1.12–7.32) for breast cancer. Test for trend was of borderline significance ($p = 0.08$). For waist/hip ratio the odds ratio was 1.89 (95% CI 0.80–4.48), (test for trend $p = 0.11$). The association between waist and breast cancer was stronger than any of the other anthropometric measurements, including weight and Quetelet's index. In postmenopausal women there was no significant interaction between age and the anthropometric variables.

Discussion

The results show that in Dutch postmenopausal women, an increased waist/hip ratio is moderately positively (but not significantly) associated with increased occurrence of breast cancer. Such an association has been observed before in one Dutch [13] and one American study [11], but not in two other studies [14, 15]. The waist circumference alone, however, was much more clearly associated with breast cancer risk than the waist/hip ratio, with a nearly threefold increased odds in the upper versus the lower tertile. The waist circumference has been suggested to be a better indicator of abdominal obesity (i.e. accumulation of visceral fat) than waist/hip ratio [18, 19]. In the postmenopausal women of the present study, Quetelet's index or weight were not significantly related to breast cancer. This result is in accordance with some other studies [6, 7], but in contrast to many other studies [2–5, 20].

In premenopausal women the association between breast cancer and waist, waist/hip ratio, and Quetelet's index depends on the age. Younger premenopausal women were more like postmenopausal women with respect to estimates of breast cancer risk than older premenopausal women were. This result, which might be influenced by selection bias, is unexpected and difficult to interpret. The absence of an unequivocal association between waist/hip ratio and breast cancer in premenopausal women is in accordance with three other studies that analysed pre- and postmenopausal women separately [13–15]. In these studies no mention has been made, however, of the presence of interaction between age and waist/hip ratio. The absence of a clear negative association between Quetelet's index or weight and breast cancer in premenopausal women is not supported by prevailing evidence from other studies [2–4, 6, 8, 15]. Interaction between age and Quetelet's index was, to our knowledge, only tested for in the study by London *et al.* These authors observed, in contrast to our results, that the inverse association between relative weight and breast cancer in premenopausal women was least marked among women 50 years of age or older [6].

A previous study in the oldest cohort of the

DOM-project showed that the association between obesity and breast cancer in postmenopausal women is much stronger in women presenting for breast cancer screening for the first time than in a group of women that has once been screened [21]. The relatively weak association between obesity and breast cancer in postmenopausal women in this study can possibly be explained by the fact that 79% of the postmenopausal women had been screened one or more times before entering this study. Almost a third of the women had been screened four times before entering this study. The association between fat distribution and breast cancer in these postmenopausal women may also be underestimated.

Among this group of postmenopausal women, the association between fat distribution and breast cancer detected at screening might be stronger than the association between fat distribution and breast cancer detected during the period of follow-up. However, the small numbers in the subgroups (16 and 22) did not allow separate analyses.

Of the premenopausal women, 97% were screened for the first time. The absence of a uniform association between obesity and breast cancer in premenopausal women cannot be explained by the number of screenings the women had undergone.

The number of screenings was almost completely determined by age and therefore not entered separately in the logistic models.

The small difference in the proportion of women with breast cancer in pre- (56/5923 = 0.94%) and postmenopausal women (38/3568 = 1.06%) is smaller than might be expected and can be explained by the fact that postmenopausal women had been screened more often before entering this study.

The discussion of the biological mechanisms underlying the relationship between body fat distribution and breast cancer will be limited to the group of postmenopausal women, in which a positive association between waist circumference and breast cancer and a suggestive positive relationship between waist/hip ratio and breast cancer was observed.

Increased aromatization of steroid precursors and reduced binding of estrogens to sex hormone binding globulin, resulting in elevated levels of biologic available estrogens, have been proposed to play a role in breast cancer etiology [13, 22, 23]. In postmenopausal women no relationship was found, however, between waist/hip ratio and serum levels of estrone, estradiol, or androstenedione [24]. Despite a negative relationship between waist/hip ratio and sex hormone binding globulin, no relationship was found between waist/hip ratio and free estradiol levels, although a curvilinear relationship between waist/hip ratio and free testosterone concentrations was found [25]. The relationship between waist/hip ratio and androgenicity was confirmed in a recent study [26]. Elevated levels of androgens have also been found to be associated with increased risk of breast cancer [27].

Hyperinsulinemia is another candidate to explain the relationship between fat distribution and breast cancer. It has already been suggested by de Waard in 1964 that postmenopausal breast cancer patients had decreased glucose tolerance [28]. More recently Berstein and Ballard-Barbash drew attention to the relationship between hyperinsulinemia and breast cancer [29, 30]. Insulin levels [9] and serum C-peptide levels, an estimate of insulin secretion [31], have been found to be elevated in breast cancer patients, and elevated insulin receptor contents have been found in human breast cancer [32]. It has been found that insulin can stimulate the growth of breast tumor cells in culture [33]. An abdominal fat distribution is positively related to increased incidence of non insulin dependent diabetes mellitus, implicating a relationship between abdominal fat distribution and impaired glucose tolerance and hyperinsulinemia [34]. Waist circumference alone was more strongly correlated to serum insulin levels than waist/hip ratio was (in premenopausal women, after adjustment of Quetelet's index) [35].

Insulin metabolism and sex hormone metabolism are interrelated and both mechanisms may therefore act together. In conclusion, our findings suggest a positive relationship between fat distribution (as measured by waist/hip ratio or by waist circumference alone) and breast cancer in postmenopausal women, whereas in premenopausal women no such relationship was observed.

Further studies are needed to clarify the biological mechanisms underlying the relationship between body fat distribution and breast cancer, with attention to menopausal status. Our finding that waist circumference alone appears to be a stronger risk factor for breast cancer than waist/hip ratio needs confirmation from other studies.

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