Waist Circumference, Waist:Hip Ratio, and Risk of Breast Cancer in the Nurses' Health Study

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This study examined prospectively the associations of waist circumference and waist:hip circumference ratio with risk of breast cancer. A total of 47,382 US registered nurses who reported their waist and hip circumferences in 1986 were followed up through May 1994 for identification of incident cases of breast cancer. During 333,097 person-years of follow-up, 1,037 invasive breast cancers were diagnosed. In proportional hazards analyses, waist circumference was nonsignificantly related to risk of premenopausal breast cancer but was significantly associated with postmenopausal breast cancer after adjustment for established breast cancer risk factors (for the highest quintile of waist circumference vs. the lowest, relative risk (RR) = 1.34; 95% confidence interval (CI): 1.05, 1.72). When the analysis was limited to postmenopausal women who had never received hormone replacement therapy, a stronger positive association was found (RR = 1.88; 95% CI: 1.25, 2.85). After the data were further controlled for body mass index, the positive association was only slightly attenuated (RR = 1.83; 95% CI: 1.12, 2.99). Among past and current postmenopausal hormone users, no significant associations were found. Similar but slightly weaker associations were observed between waist:hip ratio and breast cancer risk. These data suggest that greater waist circumference increases risk of breast cancer, especially among postmenopausal women who are otherwise at lower risk because of never having used estrogen replacement hormones. Am J Epidemiol 1999;150:1316–24.

Obesity has a complex relation to risk of breast cancer. Higher body mass index (weight (kg)/height (m)^2) is associated with a lower risk of breast cancer before menopause and with an increased risk of cancer after menopause, especially among postmenopausal women who have never received hormone replacement therapy

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Abbreviations: CI, confidence interval; MET(s), metabolic equivalent(s); RR, relative risk; SHBG, sex hormone-binding globulin.
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The Nurses’ Health Study is an ongoing US follow-up study initiated in 1976 when 121,701 female registered nurses aged 30–55 years responded to a mailed questionnaire on medical history and health behaviors. Follow-up questionnaires have been sent to participants every 2 years to identify incident cases of breast cancer and other medical events and to update information on risk factors. The follow-up rate as of 1994 was 95 percent of potential person-years. Further details on the study have been provided elsewhere (9).

For the current analysis, follow-up began in 1986, when waist and hip circumferences were reported by 50,828 women; follow-up continued through May 31, 1994. We excluded women who reported having any cancer other than nonmelanoma skin cancer prior to 1986 (n = 3,446). The analytic cohort thus included 47,382 women. Women in whom any of these conditions developed during follow-up were excluded from subsequent follow-up intervals.

Measurement of exposures

In 1986, women were asked to measure their waist circumference at the level of the umbilicus and their hip circumference at its widest location while standing in a relaxed posture. Participants were asked to record their measurements to the nearest quarter inch (6.4 mm). These circumferences were used to compute waist:hip ratio. The women were classified into quintiles of waist circumference, hip circumference, and waist:hip ratio.

Information on age, height, current weight, parity, age at first birth, family history of breast cancer (in a mother or sister), personal history of benign breast disease, age at menarche, menopausal status, age at menopause, physical activity, alcohol consumption, and postmenopausal use of hormones (primarily estrogen and/or progesterone), as well as other variables, was obtained from the 1986 questionnaire or prior questionnaires. Information on most variables was updated via biennial follow-up questionnaires. Physical activity was measured by total metabolic equivalent score. The time spent per week in a variety of physical activities was reported by the subject. The time spent in each activity was multiplied by its typical energy expenditure, expressed in terms of metabolic equivalents (METs). The resulting values were added together to yield an MET-hours/week score. Body mass index, a measure of overall obesity, was calculated as weight in kilograms divided by the square of height in meters.

Menopausal status was determined by asking women whether their menstrual periods had permanently ceased. We classified women as postmenopausal if a natural menopause or hysterectomy with bilateral oophorectomy was reported. Women who had undergone hysterectomy without bilateral oophorectomy were considered postmenopausal at more than 54 years of age for current smokers or more than 56 years of age for nonsmokers (ages at which natural menopause had occurred in 90 percent of the cohort). Women who had undergone hysterectomy without bilateral oophorectomy were considered premenopausal at less than 46 years of age for current smokers or less than 48 years of age for nonsmokers (ages at which natural menopause had occurred in only 10 percent of the cohort). At ages between these categories, women were classified as having uncertain menopausal status (10).

In a random subsample of 140 participants living in the Boston, Massachusetts area, the validity of self-reported waist and hip circumferences was assessed (11). Self-reported waist and hip circumferences and waist:hip ratio were highly correlated with technician measurements completed 6–12 months after the self-reports (Pearson correlation coefficients were 0.89, 0.84, and 0.70, respectively). On average, self-reported waist and hip circumferences were 0.05 inches (1.3 mm) and 0.54 inches (13.7 mm) smaller than technician measurements, and waist:hip ratio was 0.011 greater than technician measurements.

Ascertainment of cases

On biennial follow-up questionnaires, women were asked whether they had been diagnosed with breast cancer during the previous 2 years. We searched the National Death Index for nonrespondents to identify fatal breast cancers. For all cases identified, we requested permission from the subjects, or from next of kin for decedents, to obtain hospital records and pathology reports. Hospital records were obtained for 96 percent of the women who reported breast cancer, and self-reported breast cancers were confirmed in 99.4 percent of the records obtained. We excluded the 0.6 percent of records that did not confirm breast cancer. Because self-reports were highly accurate among those women for whom hospital records were obtained, we included women with self-reported breast
cancer for whom hospital records could not be obtained. Cases of in situ breast cancer were excluded from these analyses.

Statistical analysis

Based on clinical judgment, reported waist circumferences of >55 inches (>140 cm) or <15 inches (<38 cm) and hip circumferences of >65 inches (>165 cm) or <20 inches (<51 cm) were considered outliers and were excluded from the analyses. Follow-up started in 1986 when waist and hip circumferences were first obtained. Follow-up time was accrued up to the date of breast cancer diagnosis, the date of diagnosis of any cancer other than nonmelanoma skin cancer, the date of death, or May 31, 1994, whichever came first. Women were not included during the intervals when their menopausal status was uncertain, but they were reentered into the analyses when the information became available.

Relative risk was used as the measure of association and was computed as the incidence rate in a specific category of waist circumference, hip circumference, or waist:hip ratio divided by the rate in the reference category. We used proportional hazards analyses to adjust simultaneously for age and other potential confounders and to compute age-adjusted and multivariate-adjusted relative risks and 95 percent confidence intervals (12, 13). Tests for trend were performed by assigning the median value to each category of waist circumference, hip circumference, or waist:hip ratio and using these values to create a single continuous variable. All tests of statistical significance were two-sided.

RESULTS

During 333,097 person-years of follow-up from 1986 to 1994, 1,037 invasive breast cancers (197 in premenopausal women and 840 in postmenopausal women) were identified. The correlation matrix between waist and hip circumferences, waist:hip ratio, and body mass index among both premenopausal and postmenopausal women is shown in table 1. In age-adjusted analysis among premenopausal women, waist circumference and waist:hip ratio were not associated with risk of breast cancer (table 2). Hip circumference was significantly and inversely associated with premenopausal breast cancer risk. The relative risks were not changed materially in the primary multivariate model, which simultaneously adjusted for age, height, personal history of benign breast disease, family history of breast cancer, age at menarche, physical activity, age at first birth, and parity. The multivariate relative risk was 0.60 (95 percent confidence interval (CI): 0.37, 0.98) for the upper quintile of hip circumference versus the lowest quintile (p trend = 0.02). To examine whether the associations with body circumferences were independent of overall obesity, we added body mass index in 1986 to the primary multivariate model. After body mass index was accounted for, both waist circumference and waist:hip ratio were positively but not significantly related to risk of premenopausal breast cancer. Women in the fifth quintile of waist circumference had a relative risk of 1.74 (95 percent CI: 0.74, 4.07) compared with women in the first quintile. The relative risk was 1.43 (95 percent CI: 0.86, 2.37) for the highest quintile of waist:hip ratio compared with the lowest. The inverse relation between hip circumference and breast cancer remained significant after we accounted for 1986 body mass index. Waist circumference and hip circumference were also simultaneously entered into the primary multivariate model. After each of these variables was adjusted for the other, waist circumference tended to be positively associated with premenopausal breast cancer, and hip circumference was inversely associated; the trend test for hip circumference gave a significant result (p trend = 0.004).

In the age-adjusted analyses of postmenopausal women, waist circumference, hip circumference, and waist:hip ratio were moderately associated with increased risk of postmenopausal breast cancer (table 3). The associations did not change materially after adjustment for multiple established risk factors. The positive relation between waist circumference and risk of breast cancer was monotonic (p trend = 0.007), and the multivariate relative risk was 1.05 (95 percent CI: 1.02, 1.09) for every 2-inch (51-mm) increase in waist circumference. Compared with women in the first quintile of waist circumference, women in the fifth quintile had a multivariate relative risk of 1.34 (95 percent CI: 1.05, 1.72). After further accounting for 1986 body mass index, this association was somewhat attenuated (relative risk (RR) = 1.26; 95 percent CI: 0.88, 1.81) and was no longer significant.

<table>
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<tr>
<th>Variable</th>
<th>Waist circumference</th>
<th>Hip circumference</th>
<th>Waist:hip ratio</th>
<th>Body mass index†</th>
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<td>1.00</td>
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<td>Hip circumference</td>
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<td>0.81</td>
<td>0.34</td>
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* All correlation coefficients in the matrix were statistically significant (p < 0.001).
† Weight (kg)/height (m)².

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Controlling for hip circumference did not appreciably change the association with waist circumference. A similar and slightly weaker association was seen between waist:hip ratio and overall risk of postmenopausal breast cancer ($p$ trend = 0.005). The relative risk for the highest quintile of waist:hip ratio compared with the lowest was 1.28 (95 percent CI: 1.02, 1.61) in the primary multivariate model, but it was attenuated slightly after further accounting for 1986 body mass index ($RR = 1.22$; 95 percent CI: 0.96, 1.55). Larger hip circumference was moderately associated with a higher risk of postmenopausal breast cancer. Women in the fifth quintile of hip circumference had a multivariate relative risk of 1.29 (95 percent CI: 1.02, 1.64) compared with women in the first quintile. This association was attenuated towards the null after accounting for body mass index or waist circumference in 1986.

Because postmenopausal hormone replacement therapy greatly elevates blood hormone levels and may modify the association between adiposity and postmenopausal breast cancer (1), we performed analyses stratified by postmenopausal hormone use (figure 1). Among women who had never used postmenopausal hormones (322 breast cancer cases and 102,586 person-years), there was a stronger positive association between waist circumference and postmenopausal breast cancer. The multivariate relative risks for the fourth and fifth quintiles of waist circumference were 1.52 (95 percent CI: 1.02, 2.27) and 1.88 (95 percent CI: 1.25, 2.85) in comparison with the first quintile. The associations were only slightly attenuated after accounting for body mass index or waist circumference in 1986.


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<th>RR adjusted for waist or hip circumference§</th>
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<td>0.86, 2.37</td>
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</table>

* RR, relative risk.
† Adjusted for age (continuous variable), height (continuous variable), personal history of benign breast disease (yes/no), family history of breast cancer (yes/no), age at menarche (≤10, 11–12, 13, 14, or ≥15 years), physical activity (total metabolic equivalent score of ≤2.2, 2.3–4.9, 5.0–10.9, 11.0–22.9, or ≥23.0), age at first birth (nulliparous and ≤24, 25–29, or ≥30 years), and parity (nulliparous and 1–2, 3–4, or ≥5 births).
‡ Adjusted for body mass index (weight (kg)/height (m)^2) in 1986 (continuous variable) in addition to the above variables.
§ Relative risks for waist and hip circumference were adjusted for each other in addition to the above variables, excluding body mass index in 1986.
¶ 1 inch = 25.4 mm.
# Reference category.

* Am J Epidemiol Vol. 150, No. 12, 1999

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<th>Multivariate RR†</th>
<th>95% confidence interval</th>
<th>RR adjusted for body mass index‡</th>
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<th>RR adjusted for waist or hip circumference§</th>
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<td>0.91, 1.46</td>
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<td>1.24</td>
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<td>39,370</td>
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<td>1.02, 1.65</td>
<td>1.34</td>
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<td>1.26</td>
<td>0.88, 1.81</td>
<td>1.32</td>
<td>0.96, 1.82</td>
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*p for trend 0.01 0.007 0.15 0.05

| Hip circumference (inches) |                        |                           |                  |                         |                 |                         |                               |                         |                                           |                         |
| 20.0–36.9          | 125                    | 44,814                    | 1.00#            | 1.00#                   | 1.00#          | 1.00#                   |                               |                         |                                           |                         |
| 37.0–38.4          | 177                    | 51,753                    | 1.22             | 0.97, 1.54              | 1.15           | 0.92, 1.45              | 1.12                          | 0.89, 1.42              | 1.11                          | 0.88, 1.40              |
| 38.5–40.4          | 204                    | 58,456                    | 1.22             | 0.98, 1.53              | 1.14           | 0.91, 1.43              | 1.07                          | 0.84, 1.37              | 1.04                          | 0.82, 1.32              |
| 40.5–42.9          | 153                    | 45,096                    | 1.18             | 0.93, 1.50              | 1.08           | 0.85, 1.38              | 0.98                          | 0.75, 1.29              | 0.93                          | 0.71, 1.21              |
| 43.0–65.0          | 181                    | 46,637                    | 1.35             | 1.08, 1.70              | 1.29           | 1.02, 1.64              | 1.07                          | 0.76, 1.51              | 0.98                          | 0.71, 1.34              |

*p for trend 0.02 0.06 0.71 0.84

| Waist:hip ratio    |                        |                           |                  |                         |                 |                         |                               |                         |                                           |                         |
| <0.73             | 132                    | 46,332                    | 1.00#            | 1.00#                   | 1.00#          | 1.00#                   |                               |                         |                                           |                         |
| 0.73–0.75         | 142                    | 44,751                    | 1.07             | 0.85, 1.36              | 1.08           | 0.85, 1.37              | 1.08                          | 0.85, 1.37              |                                           |                         |
| 0.76–0.79         | 190                    | 56,114                    | 1.02             | 0.82, 1.28              | 1.04           | 0.83, 1.31              | 1.02                          | 0.81, 1.28              |                                           |                         |
| 0.80–0.83         | 198                    | 48,118                    | 1.33             | 1.07, 1.67              | 1.38           | 1.10, 1.73              | 1.34                          | 1.06, 1.68              |                                           |                         |
| ≥0.84             | 188                    | 49,440                    | 1.19             | 0.95, 1.50              | 1.28           | 1.02, 1.61              | 1.22                          | 0.96, 1.55              |                                           |                         |

*p for trend 0.03 0.005 0.03

* RR, relative risk.
† Adjusted for age (continuous variable), height (continuous variable), personal history of benign breast disease (yes/no), family history of breast cancer (yes/no), age at menarche (50–10–10, 13, or 15 years), physical activity (total metabolic equivalent score of ≤2.2, 2.3–4.9, 5.0–10.9, 11.0–22.9, or ≥23.0), age at first birth (nulliparous and 25–29, or ≥30 years), age at menopause (≤44, 45–49, 50–54, or ≥55 years), postmenopausal hormone use (never, current, or past), and parity (nulliparous and 1–2, 3–4, or ≥5 births).
‡ Adjusted for body mass index (weight [kg]/height [m]²) in 1986 (continuous variable) in addition to the above variables.
§ Relative risks for waist and hip circumference were adjusted for each other in addition to the above variables, excluding body mass index in 1986.
¶ 1 inch = 25.4 mm.
# Reference category.

Further adjustment for 1986 body mass index (for the fourth and fifth quintiles, RR = 1.50 (95 percent CI: 0.98, 2.29) and RR = 1.83 (95 percent CI: 1.12, 2.99), respectively). Among current postmenopausal hormone users (329 breast cancer cases and 86,821 person-years), no association was observed between waist circumference and risk of postmenopausal breast cancer. This null association remained after further adjustment for body mass index. Among postmenopausal women who had used hormones in the past (182 breast cancer cases and 54,785 person-years), the magnitude of the association with waist circumference was intermediate. The interaction between waist circumference and postmenopausal hormone use was of borderline significance (p = 0.06, 2 df). For waist:hip ratio, the interaction with postmenopausal hormone use was statistically significant (p = 0.03, 2 df) (figure 2).

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Among never users of postmenopausal hormones, a strong positive association was observed between waist:hip ratio and postmenopausal breast cancer (for the highest quintile of waist:hip ratio vs. the lowest, multivariate RR = 1.85 (95 percent CI: 1.25, 2.74)), while among current and past users of postmenopausal hormones, there was no clear dose-response relationship between waist:hip ratio and risk of breast cancer. After further accounting for body mass index, the magnitude of the association with postmenopausal breast cancer became somewhat weaker in general.

We also examined the associations between waist circumference, waist:hip ratio, and breast cancer risk within the strata of other risk factors, including age, body mass index, and family history of breast cancer, but we did not observe any significant effect modification by these factors. Among women with a family his-
Body Fat Distribution and Breast Cancer

1st 2nd 3rd 4th Quintile of Waist Circumference

FIGURE 1. Relative risk of breast cancer by hormone use (never, past, or current) and quintile of waist circumference among postmenopausal women, Nurses' Health Study, 1986–1994. Relative risks were adjusted for age, height, personal history of benign breast disease, family history of breast cancer, physical activity, age at menarche, age at first birth, age at menopause, and parity.

For those women with a family history of breast cancer (117 breast cancer cases), the multivariate relative risks for the fifth quintile versus the first quintile were 1.23 (95 percent CI: 0.65, 2.34) for waist circumference and 0.73 (95 percent CI: 0.40, 1.33) for waist:hip ratio. Among those women without a family history (693 breast cancer cases), these rela-

FIGURE 2. Relative risk of breast cancer by hormone use (never, past, or current) and quintile of waist:hip ratio among postmenopausal women, Nurses' Health Study, 1986–1994. Relative risks were adjusted for age, height, personal history of benign breast disease, family history of breast cancer, physical activity, age at menarche, age at first birth, age at menopause, and parity.

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tive risks were 1.45 (95 percent CI: 1.10, 1.92) for waist circumference and 1.40 (95 percent CI: 1.09, 1.81) for waist:hip ratio.

We conducted additional analyses to adjust for alcohol consumption; this did not appreciably change the associations of waist circumference, hip circumference, and waist:hip ratio with breast cancer risk in either premenopausal or postmenopausal women. We also examined 1986 body mass index and risk of breast cancer after adjusting for multiple covariates and waist circumference or waist:hip ratio. Consistent with our previous findings (1), body mass index was inversely associated with premenopausal breast cancer but was positively associated with postmenopausal breast cancer, especially among women who had never used postmenopausal hormones.

**DISCUSSION**

In this study, waist circumference and waist:hip ratio were moderately associated with a higher risk of breast cancer, particularly among postmenopausal women. Even after accounting for overall adiposity as measured by body mass index, greater waist circumference and waist:hip ratio were still associated with an additional modest to moderate impact on breast cancer risk. The positive associations were much stronger among postmenopausal women who had never received hormone replacement therapy. Greater hip circumference was associated with a lower risk of premenopausal breast cancer but was not related to postmenopausal breast cancer after we accounted for overall obesity.

In a few case-control studies, waist:hip ratio has been found to be a risk factor for breast cancer in premenopausal women (14). However, in most case-control studies that have examined regional adiposity, the associations between waist circumference, waist:hip ratio, and risk of premenopausal breast cancer have been weak and equivocal (3, 4, 15). In one large population-based case-control study, body fat distribution measured by waist:hip ratio or subscapular:triceps skinfold ratio was not related to breast cancer in women under age 45 years (16).

Central adiposity assessed by waist circumference or waist:hip ratio has been associated with postmenopausal breast cancer, independently of relative weight, in several studies (14, 17, 18). In two case-control studies in the Netherlands in which breast cancer cases were detected at breast cancer screening or afterwards, waist circumference and waist:hip ratio were positively associated with postmenopausal breast cancer (4). The estimated relative risks were 1.89 (95 percent CI: 0.80, 4.48) for waist:hip ratio and 2.86 (95 percent CI: 1.12, 7.32) for waist circumference (upper tertile vs. lower) (3). However, others have noted no difference in waist:hip ratio between cases and controls (15). Body fat distribution was also assessed by contrasting groups of subscapular and triceps skinfold thicknesses; no relation between fat distribution and breast cancer was found among postmenopausal women (19).

Four prospective studies have examined regional adiposity and risk of breast cancer (5–8). In the Framingham cohort study, a central adiposity ratio was computed as the sum of skinfold measurements from the upper and lower trunk divided by the sum of skinfold measurements from the upper and lower extremities. Risk of breast cancer was significantly associated with truncal fat predominance; the relative risks for the fourth quintile of central adiposity ratio versus the first quintile were 1.2 (95 percent CI: 0.6, 2.4) among premenopausal women and 2.1 (95 percent CI: 1.0, 4.6) among postmenopausal women. The positive association between central adiposity and breast cancer risk was not altered after adjustment for overall adiposity (5). In the Dutch "DOM" cohort (7), after a median follow-up period of 10.6 years, risk of breast cancer was positively and significantly associated with waist:hip ratio (RR = 2.63 for upper quartile vs. lower quartile) among women with natural menopause, and this association did not change after adjustment for height and weight.

In the Iowa Women's Health Study, abdominal adiposity as assessed by waist:hip ratio was associated with an increased risk of postmenopausal breast cancer; the odd ratio for the highest tertile versus the lowest was 1.39 (95 percent CI: 0.99, 1.96) (6). In a later report on the same cohort, the association between waist:hip ratio and breast cancer risk was more pronounced among women with a positive family history of breast cancer. The age-adjusted relative risk for the fifth quintile of waist:hip ratio compared with the first quintile was 3.24 (95 percent CI: 2.11, 4.99) in women with a family history of breast cancer (83 breast cancer cases) and 1.20 (95 percent CI: 0.87, 1.67) in women without such a family history (382 breast cancer cases) (20). However, we did not find evidence for such an interaction in this study.

In another report from the Dutch DOM cohort (8), body fat distribution, assessed by contrasting subscapular and triceps skinfold thicknesses, was not related to breast cancer incidence among postmenopausal women, perhaps because the measure did not include an indicator of gluteofemoral fatness, as was used in other studies. The larger error associated with skinfold thickness measurement may also have contributed to the null association.

In most previous studies, a weaker association between central obesity and breast cancer risk has been
seen among premenopausal women than among postmenopausal women, and this was true in our primary analyses. After adjustment for overall obesity as measured by body mass index, the association became stronger among premenopausal women but the confidence intervals were wider. The weaker association between regional adiposity and breast cancer in premenopausal women may be explained by different sources of endogenous sex hormones before and after menopause (21, 22).

In our study cohort, waist circumference was highly correlated with body mass index (correlation coefficient = 0.82), and body mass index was inversely associated with premenopausal breast cancer and positively associated with postmenopausal breast cancer (1); thus, after controlling for body mass index, the association between waist circumference and breast cancer became more positive among premenopausal women and was attenuated among postmenopausal women. Nevertheless, our data indicated that central adiposity still had an additional moderate association with breast cancer risk after we accounted for overall obesity. However, neither overall obesity assessed by body mass index nor central obesity assessed by waist circumference are measured perfectly (23). Because they are highly correlated, they may in part serve as surrogates for each other. Thus, it is possible that an apparently independent effect of waist circumference on breast cancer risk that remains after adjustment for body mass index could be due to additional information being conveyed by waist circumference about overall adiposity, rather than a specific effect of body fat distribution.

In our study, waist circumference was a slightly stronger predictor of breast cancer than was waist:hip ratio. Waist circumference is a fairly unambiguous measure of abdominal fat, whereas the interpretation of waist:hip ratio is complicated because it is the ratio of two variables, both of which could contribute to breast cancer risk (23). In addition, waist:hip ratio has more measurement error because it includes two sources of error, i.e., error from both waist and hip measurements (10). Waist circumference has been more strongly correlated with body mass index and the percentage of body fat measured by bioelectric impedance analysis or dual-energy X-ray absorptiometry than has waist:hip ratio (24). Thus, waist circumference seems to be a slightly better variable for reflecting abdominal adiposity.

The reason for the inverse association between hip circumference and risk of premenopausal breast cancer is unclear. Hip circumference reflects both muscle and fat, as well as bony structure. The inverse association with hip circumference that persists after adjustment for body mass index or waist circumference may suggest that more muscle and/or larger bones are associated with lower risk of premenopausal breast cancer.

Central adiposity is associated with a decrease in sex hormone-binding globulin (SHBG) concentration (25). The percentage of serum estradiol bound to SHBG closely follows SHBG concentration, so a more central body fat distribution has been significantly related to greater bioavailability of estradiol (4, 26). In addition, women with abdominal adiposity have increased levels of free fatty acids and triglycerides (27–29), which increases the level of bioavailable estrogen by displacing estrogen from SHBG to albumin, where it is less tightly bound (26). Thus, both decreases in SHBG and increases in free fatty acids and triglycerides result in increases in free estradiol levels in both premenopausal and postmenopausal women. Furthermore, it has been proposed that abdominal adiposity is associated with an excess of androgen and increased conversion of androgen to estrogen in adipose tissue (30). Abdominal obesity is also associated with hyperinsulinemia and insulin resistance, which have been hypothesized to be associated with an increased risk of breast cancer (31, 32).

Postmenopausal hormone use partially masked the association between central obesity and postmenopausal breast cancer, probably because exogenous hormone use elevated blood hormone levels among both lean and obese women; as a result, all postmenopausal hormone users were at increased risk of breast cancer regardless of central obesity (see figures 1 and 2). Only among never users of postmenopausal hormones, in whom blood hormone levels had never been influenced by exogenous hormones, was a strong positive association between abdominal obesity and postmenopausal breast cancer observed. This relation, also seen with overall adiposity (1), strongly suggests that the increased risks of breast cancer associated with both overall and regional adiposity are primarily mediated by higher endogenous estrogen exposure among postmenopausal women.

In conclusion, we found waist circumference to be associated with a moderately increased risk of breast cancer, especially among postmenopausal women who had never received hormone replacement therapy. This adverse impact on breast cancer risk appears to be partly independent of overall adiposity, and to be mediated largely through greater exposure to endogenous estrogens.

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