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BODY SIZE AND BREAST CANCER RISK: FINDINGS FROM THE EUROPEAN PROSPECTIVE INVESTIGATION INTO CANCER AND NUTRITION (EPIC)

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Abbreviations: BMI, body mass index; CI, confidence interval; EPIC, European Prospective Investigation into Cancer and Nutrition; HRT, hormone replacement therapy; NHS, Nurses' Health Study; OC, oral contraceptive; RR, relative risk; SHBG, sex hormone–binding globulin; WHI, Women's Health Initiative; WHR, waist–hip ratio.

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The evidence for anthropometric factors influencing breast cancer risk is accumulating, but uncertainties remain concerning the role of fat distribution and potential effect modifiers. We used data from 73,542 premenopausal and 103,344 postmenopausal women from 9 European countries, taking part in the EPIC study. RRs from Cox regression models were calculated, using measured height, weight, BMI and waist and hip circumferences; categorized by cohort-wide quintiles; and expressed as continuous variables, adjusted for study center, age and other risk factors. During 4.7 years of follow-up, 1,879 incident invasive breast cancers were identified. In postmenopausal women, current HRT modified the body size–breast cancer association. Among nonusers, weight, BMI and hip circumference were positively associated with breast cancer risk (all $p_{trend} \leq 0.002$); obese women (BMI > 30) had a 31% excess risk compared to women with BMI < 25. Among HRT users, body measures were inversely but nonsignificantly associated with breast cancer. Excess breast cancer risk with HRT was particularly evident among lean women. Pooled RRs per height increment of 5 cm were 1.05 (95% CI 1.00–1.16) in premenopausal and 1.10 (95% CI 1.05–1.16) in postmenopausal women. Among premenopausal women, hip circumference was the only other measure significantly related to breast cancer ($p_{trend} = 0.03$), after accounting for BMI. In postmenopausal women not taking exogenous hormones, general obesity is a significant predictor of breast cancer, while abdominal fat assessed as waist–hip ratio or waist circumference was not related to excess risk when adjusted for BMI. Among premenopausal women, weight and BMI showed nonsignificant inverse associations with breast cancer.

Key words: *breast neoplasm; obesity; fat distribution; body weight; height; hormone replacement therapy*

Numerous studies have investigated the relation between indicators of body size and breast cancer incidence.[1–6] Findings on attained height in relation to breast cancer occurrence from diverse populations consistently suggest that taller women are at increased risk for breast cancer irrespective of menopausal status.[2,7,8] Despite a number of generally accepted risk characteristics, the association between body weight and breast cancer remains complex. The relation is modified by menopausal status, with a higher weight or BMI associated with reduced risk in premenopausal women and increased risk in postmenopausal women. Moreover, results from studies on associations between body weight and breast cancer differ to some extent according to study design. Case-control studies have tended to report significant positive associations between weight or BMI and postmenopausal breast cancer risk, whereas results from cohort studies are less consistent.[2,9] Among premenopausal women, inverse associations with BMI have been found in most cohort studies but both inverse and direct associations have been reported in case-control studies.[1,10,11]

Increased central adiposity that primarily occurs during or after menopause may be a more specific marker of the metabolic consequences of obesity and a better indicator of risk than body weight in itself.[12,13] However, results on the role of fat distribution in postmenopausal breast cancer risk are equivocal.[1,14] An IARC review also concluded that central adiposity, assessed as either waist circumference or WHR, is not predictive of premenopausal breast cancer risk.[1]

Special attention has been given to the effects of adiposity on estrogen metabolism as an underlying biologic mechanism for the body size–breast cancer association. There is substantial evidence that high concentrations of endogenous estrogen are associated with increased risk of postmenopausal breast cancer.[15–17] Accordingly, the increased risk of breast cancer in overweight postmenopausal women is usually attributed to both excess plasma levels of estrogen derived from aromatization of androgens in peripheral fat depots and decreased SHBG.[5,18,19] In contrast, overweight premenopausal women tend to have more irregular menstrual cycles and increased rates of anovulatory infertility, suggesting that fewer ovulatory cycles and less cumulative exposure to estrogens and progesterone may reduce risk.[1,3]

Moreover, observations indicating significantly increased risk in women using exogenous sex steroids, such as HRT, further establish the role of hormones in the etiology of breast cancer.[20–23] Use of menopausal hormones can obscure the effect of adiposity on breast cancer risk by influencing estrogen levels.[1,3] An effect modification by HRT has been reported by only a few prospective studies from the United States,[14,24,25] the Pooling Project on Diet and Cancer[26] and case-control studies,[27–29] indicating a stronger impact of high BMI, weight gain or measures of fat distribution on breast cancer risk among postmenopausal women who never used exogenous hormones.

Our purpose was to *(i)* estimate the RR of pre- and postmenopausal breast cancer in relation to various anthropometric measures of general (weight, BMI) and central (weight circumference, WHR) obesity, controlling for other known risk factors in female study participants from EPIC, and *(ii)* evaluate whether the associations between these body measures and risk of postmenopausal breast cancer are modified by exogenous hormone use at baseline.

MATERIAL AND METHODS

EPIC is a multicenter prospective cohort study designed primarily to investigate the relation between nutrition and cancer. The EPIC cohort consists of subcohorts recruited in 23 administrative centers in 10 European countries: Denmark, France, Germany, Greece, Italy, the Netherlands, Norway, Spain, Sweden and the United Kingdom, allowing comparisons among regions with very different rates of cancer occurrence and distributions of lifestyle and food habits. Food-related and lifestyle questionnaires were administered and anthropometric measurements obtained from all participants at the time of enrollment (1992–2000). The 519,978 eligible male and female participants were mostly aged 25–70 years and recruited from the general population residing in a given geographic area, *i.e.,* a town or province.[30] Exceptions were the French cohort (based on female members of the health insurance for school employees), the Utrecht cohort in the Netherlands (based on women attending breast cancer screening), the Ragusa cohort in Italy (based on blood donors and their spouses) and the Oxford cohort in the United Kingdom (based on vegetarian volunteers and healthy eaters). Eligible subjects were invited to participate in the study, and those who accepted gave informed consent and completed questionnaires on their diet, lifestyle and medical history. Subjects were then invited to a center to provide a blood sample and to have anthropometric measurements taken. The methods have been reported in full by Riboli *et al.*[30,31]

Study population

The present study was based on data from 336,053 female participants after *a priori* excluding women with prevalent cancer at any site at baseline examination, if they had missing dietary or nondietary questionnaire data or were in the top or bottom 1% of the ratio of energy intake to estimated energy requirement (calculated from age and body weight), to reduce the impact on the analysis of implausible extreme values. The original cohort (n = 336,053) was further restricted to 235,486 women with measured or predicted (Oxford, "health-conscious" group) anthropometric characteristics, thus excluding women from Norway (n = 35,236) or Umeå, Sweden (n = 12,267), and 70% of the French female cohort (n = 48,161) for whom only self-reported data on body size were available. Another 4,903 women had missing values on their measured body characteristics. Women were classified according to menopausal status at enrollment based on an algorithm that accounts for complete and combined information on menstrual status/history, type of menopause (natural, bi-/unilateral oophorectomy, hysterectomy), use of OCs and menopausal hormones. Based on menstrual status over the past 12 months, not obscured by pill or hormone use, women were categorized as follows: postmenopausal (no menstrual cycles), perimenopausal (1–9 menstrual cycles) or premenopausal (≥10 menstrual cycles). Age cut-offs (premenopausal, <42 years; perimenopausal, 42–55 years; postmenopausal, >55 years) were applied when data on the above-mentioned characteristics were either insufficient or lacking (total 1% of women with measured body characteristics). On the basis of the algorithm, 31.8% were premenopausal and 45.5% were naturally postmenopausal. Women who were perimenopausal (15.3%), had undergone surgical menopause (3.5%) or were of uncertain menopausal status (3.9%) were excluded from analysis, as were subjects with missing data on current hormone use or OC use and women aged >80 years at baseline. The analytic cohort therefore consisted of 176,886 women from 9 countries, 73,542 premenopausal and 103,344 naturally postmenopausal.

End points and ascertainment of cases

Incident breast cancer cases were identified by population cancer registries (Denmark, Italy, the Netherlands, Spain, Sweden, the United Kingdom) or by active follow-up (France, Germany, Greece), depending on the follow-up system in each of the participating countries. Active follow-up used a combination of methods, including health insurance records, cancer and pathology registries and direct contact of participants or next-of-kin. Mortality data were also obtained from cancer or mortality registries at the regional or national level. Women were followed from study entry (1992–2000) until first breast cancer diagnosis, death, emigration or end of the follow-up period. By the end of November 2002, 4,261 breast cancer cases (invasive $n = 3{,}805$, *in situ* $n = 452$, unspecified $n = 4$) had been reported to the common database at the IARC, based on information on complete follow-up data for the follow-up period between 31 December 1999 and 31 December 2000 in most of the centers. Mortality data were coded according to the ICD-10 and cancer incidence data, according to ICD-O-2. This analysis included 1,879 invasive (primary, malignant) breast cancer cases, 474 of whom were premenopausal and 1,405 postmenopausal at enrollment.

Classification of body measures and other predictor variables

Weight and height were measured to the nearest 0.1 kg and 0.1 or 0.5 cm, respectively, with subjects wearing no shoes, in participating centers.[32] Waist circumference was measured either at the narrowest torso circumference (France; Italy; Spain; the United Kingdom; Utrecht, the Netherlands; Heidelberg, Germany; Greece) or at the midpoint between the lower ribs and iliac crest (Spain; Bilthoven, the Netherlands; Greece; Germany; Malmö, Sweden). In Spain, Greece, Denmark and Heidelberg (Germany), a combination of methods was used, although the majority of participants were measured at the narrowest circumference. Hip circumference was measured at the widest circumference (France; Italy; Spain; Bilthoven, the Netherlands; Greece; Malmö, Sweden) or over the buttocks (UK; Utrecht, the Netherlands; Germany; Denmark).

For the present study, body weight and waist and hip circumferences were adjusted to reduce heterogeneity due to protocol differences in clothing worn during measurement.[32] For the "health-conscious" group based in Oxford (UK), linear regression models were used to predict sex- and age-specific values from women with both measured and self-reported body measures as previously described.[32,33] BMI was calculated as weight divided by height (kg/m^2). Subjects with BMI between 25.0 and 29.9 kg/m^2 were classified as overweight and those with BMI ≥30.0 kg/m,[2] as obese.[34] The waist and hip circumferences of each participant were used to construct a WHR (cm/cm).

Information on reproductive, sociodemographic and lifestyle characteristics was obtained from the standardized health questionnaire at study entry. Other known risk factors included in this analysis were age at menarche (≤11, 12, 13, 14, ≥15 years), age at first pregnancy (first birth <20, 20–30, >30 years, nulliparous), education (none, primary school, technical/professional school, secondary school, university), smoking status (never, former, current), alcohol consumption (abstainers, 1–14, 15–30, >30 g ethanol/day), current OC use (no/yes) and current hormone use (no/yes). Current hormone use refers to use of menopausal hormones at the time of recruitment, queried by questionnaire or during interviews. Information on hormone use was derived from country-specific questionnaire items and combined in a dichotomous variable (no/yes). The nonuser group at baseline included 17% former users. Current hormone use included estrogen preparations or combined estrogen/progestin preparations and is referred to as "HRT use" throughout this report.

Statistical analysis

Cox proportional hazards models were used to estimate adjusted RRs and 95% CIs of breast cancer incidence for each body measure category. Age was used as the underlying (primary dependent) time variable in the counting process, with entry time (t_0) defined as the subject's age in days at recruitment and exit time (t_1) defined as the subject's age in days at breast cancer diagnosis or censoring. Subjects were categorized according to quintiles of height, weight, BMI, waist and hip circumferences and WHR defined over the entire cohort, using the first quintile as the reference category. All multivariate models were stratified (option "strata" in the PHREG procedure; SAS Institute, Cary, NC) by age at recruitment and by study center to be less sensitive against violations of the proportional hazards assumption, and simultaneously adjusted for the following established breast cancer risk factors: height and BMI (as continuous variables), age at menarche, parity, age at first birth, education, smoking status, alcohol consumption, current HRT use and OC use. Mutual adjustment of body measures (*e.g.,* weight adjusted for height, waist and hip circumferences and WHR adjusted for BMI) was also examined. An indicator category for missing responses for each covariate was created to minimize loss of observation due to missing covariate data.

Trend tests were calculated using quintile-based scores, assigning a score of 1–5 to an individual according to the interquintile interval of the selected body measure. For country-specific analyses, body measures were treated as continuous variables. To estimate the overall effect across countries, the method of DerSimonian and Laird,[35] based on the random effects model, was used. Heterogeneity between country-specific RRs was assessed by Cochran's χ^2 test.[36]

To examine the potential effect modification of the body size–breast cancer association by current HRT use, interaction terms for each body measure with HRT use were tested. A p value for interaction was calculated, referring to the interaction term of the dichotomous HRT variable and the anthropometric trend variable (quintile-based score) over the entire cohort of postmenopausal women. All tests of statistical significance were 2-sided, and $p < 0.05$ was considered significant. Statistical analyses were performed with the PHREG procedure in the SAS software package, version 8.

RESULTS

The analytic cohort of 176,886 women, aged 18–80 years at baseline, was followed from 1992 for an average of 4.7 (±1.7) years, for a total of 832,620 person-years. Table I gives the cohort characteristics of the participants stratified by menopausal status. Median age at breast cancer diagnosis was 45.0 years for premenopausal and 64.0 years for postmenopausal women.

Table II shows the mean height, body weight, BMI and waist and hip circumferences in each of the participating countries. Women from Spain and Greece were the shortest and tended to have the highest relative weight and largest waist and hip circumferences. Women from the Netherlands were the tallest and French women, the most lean. This pattern was also reflected by the prevalence of obesity (BMI > 30.0), which averaged 15.3% for the entire cohort but differed substantially by country. Cohorts from Greece (35.5%) and Spain (29.3%) had the highest proportion of obese women, while those from France (5.8%) and the United

TABLE I – COHORT CHARACTERISTICS BY MENOPAUSAL STATUS, THE EPIC STUDY

Country	Premenopausal				Postmenopausal			
	Cohort size (n)[1]	Age, censored median (years, range)	Person-years	Number of cases[2]	Cohort size (n)[1]	Age, censored median (years, range)	Person-years	Number of cases[2]
France	3,266	53 (44–62)	21,324.6	79	7,395	65 (47–75)	47,284.0	185
Italy	10,596	47 (32–62)	46,739.1	103	12,363	62 (40–81)	54,232.0	149
Florence	2,922	49 (34–62)	16,350.2	51	4,587	62 (45–74)	23,117.6	65
Varese	3,622	49 (37–61)	17,241.9	40	3,610	63 (47–81)	17,270.0	56
Ragusa	1,878	44 (35–59)	6,049.5	5	735	59 (43–73)	2,356.0	7
Turin	1,452	47 (36–60)	4,554.1	6	1,612	60 (40–72)	4,747.2	10
Naples	722	43 (32–47)	2,543.4	1	1,819	60 (42–78)	6,741.3	11
Spain	12,949	48 (34–62)	75,267.9	92	7,743	64 (45–75)	44,540.0	82
Asturias	2,940	48 (35–62)	19,023.3	24	1,417	64 (47–73)	9,221.6	15
Granada	2,759	47 (36–61)	14,386.0	13	2,065	63 (46–73)	10,479.7	19
Murcia	2,915	47 (34–60)	15,553.7	13	1,686	63 (45–75)	8,894.8	9
Navarra	2,044	49 (34–62)	13,074.3	18	1,309	64 (45–74)	8,677.5	24
San Sebastian	2,291	48 (40–62)	13,230.8	24	1,266	63 (46–72)	7,267.0	15
UK	22,873	41 (22–62)	103,114.6	102	17,400	66 (42–86)	84,214.6	238
Cambridge	1,689	53 (43–62)	8,398.6	17	7,446	68 (48–84)	39,160.7	117
Oxford, general[3]	1,341	51 (41–62)	7,585.4	21	2,167	63 (44–80)	11,674.9	52
Oxford, health[3]	19,843	39 (22–61)	87,130.6	64	7,787	64 (42–86)	33,379.0	72
Netherlands	8,536	41 (22–62)	31,791.5	51	12,544	64 (43–77)	63,591.1	185
Bilthoven	7,296	39 (22–60)	25,546.2	29	2,054	61 (43–71)	7,393.2	15
Utrecht	1,240	59 (50–62)	6,245.3	22	10,490	65 (50–77)	56,197.9	167
Greece	5,271	44 (24–59)	19,550.7	9	7,499	67 (43–84)	27,663.8	24
Germany	8,049	42 (24–61)	32,575.2	19	9,744	63 (41–77)	41,682.8	98
Heidelberg	3,393	42 (36–60)	11,524.6	8	4,426	62 (41–71)	16,577.9	59
Potsdam	4,656	42 (24–61)	21,050.6	11	5,318	64 (42–77)	25,104.9	39
Sweden[4]	—	—	—	—	9,012	69 (50–79)	67,469.5	211
Denmark	2,002	55 (52–60)	6,307.8	19	19,644	62 (51–71)	65,270.5	233
Aarhus	736	54 (52–59)	2,208.1	7	5,653	61 (52–69)	18,108.9	49
Copenhagen	1,266	55 (52–60)	4,099.8	12	13,991	62 (51–71)	47,161.6	184
Total	73,542	45 (22–62)	336,671.4	474	103,344	64 (40–86)	495,948.8	1,405

[1]Women with complete measured anthropometric characteristics.–[2]Invasive (malignant, primary) breast cancer.–[3]The Oxford cohort consists of participants recruited from both the general population and "health-conscious" individuals (vegetarians and healthy eaters).–[4]Sweden: data presented are based on the Malmö cohort; data on premenopausal women not available.

TABLE II – MEAN HEIGHT, WEIGHT, BMI, WAIST CIRCUMFERENCE, HIP CIRCUMFERENCE, AND WHR AT BASELINE EXAMINATION IN 176,886 WOMEN, THE EPIC STUDY

Country	Cohort number	Height (cm)		Weight (kg)		BMI (kg/m^2)		Waist (cm)		Hip (cm)		WHR (cm/cm)	
		Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
France	10,661	160.4	5.9	60.4	10.2	23.5	3.8	77.1	9.6	98.4	8.3	0.784	0.074
Italy	22,959	158.6	6.2	64.1	11.0	25.5	4.3	79.6	10.6	100.2	8.7	0.794	0.070
Spain	20,692	156.9	5.9	68.7	11.3	28.0	4.7	86.9	11.2	105.5	9.5	0.822	0.062
UK	40,273	163.4	6.2	63.9	11.1	24.0	4.1	76.0	9.2	99.1	7.9	0.766	0.059
Netherlands	21,080	164.9	6.5	67.9	11.4	25.0	4.1	80.4	10.6	102.0	8.5	0.787	0.065
Greece	12,770	156.3	6.8	69.5	12.6	28.5	5.3	87.5	12.8	106.9	10.0	0.817	0.083
Germany	17,793	163.4	6.3	68.1	12.5	25.5	4.7	80.8	11.7	101.3	9.3	0.796	0.070
Sweden	9,012	162.8	6.0	67.4	11.7	25.4	4.3	78.7	10.7	98.8	9.6	0.795	0.054
Denmark	21,646	163.9	6.0	68.6	12.0	25.5	4.3	82.0	11.1	101.6	8.8	0.806	0.073
Total	176,886	161.5	6.9	66.3	11.8	25.5	4.6	80.5	11.3	101.4	9.2	0.793	0.070

Kingdom (8.1%) had the lowest. For the other countries, the prevalence of obesity was about 11–16%.

Premenopausal women

Height was positively but not significantly associated with breast cancer risk (Table III). Body weight and BMI were inversely related to breast cancer incidence, but none of the risk estimates approached statistical significance (Table IV). Using the WHO classification for overweight and obesity, risks were lower by 12% and 11% in the 25.0–29.9 category (RR = 0.88, 95% CI 0.70–1.10) and the ≥30.0 category (RR = 0.89, 95% CI CI 0.64-1.22), respectively, compared to women in the normal BMI range (<25.0) (data not shown).

Measures of central adiposity, such as WHR and waist and hip circumferences, were not associated with breast cancer risk. However, after additional adjustment for BMI, both waist and hip circumferences were associated with a significant increase in premenopausal women. Those in the highest quintile of waist (≥89.3 cm) or hip (≥108.0 cm) circumference had a significant 81% or 70% increased risk, respectively, compared to women in the lowest quintiles.

Table V shows the country-specific and pooled adjusted RRs for each anthropometric measure (as continuous variable) by menopausal status. The association between hip circumference and premenopausal breast cancer risk remained significant, corresponding to a 2% increased risk per 1 cm increment in hip circumference, after adjustment for BMI and was similar in all countries. None of the other anthropometric measures was significantly related to premenopausal breast cancer risk. There was no statistical evidence of heterogeneity between countries for any of the selected body measures.

Postmenopausal women

There was a significant elevation in breast cancer risk with increasing height ($p_{\text{trend}} < 0.001$) among postmenopausal women (Table III). Women in the category 163.5–167.6 cm had the

TABLE III – MULTIVARIATE-ADJUSTED RR OF BREAST CANCER IN 176,886 WOMEN ACCORDING TO HEIGHT STRATIFIED BY MENOPAUSAL STATUS, THE EPIC STUDY

Height[1] (cm)	Premenopausal (n = 73,542)			Postmenopausal (n = 103,344)		
	Cases	RR[2]	CI	Cases	RR[3]	CI
<156.0	84	Reference		266	Reference	
156.0–159.9	101	1.17	0.87–1.57	279	1.10	0.93–1.31
160.0–163.4	103	1.28	0.95–1.72	280	1.29	1.08–1.54
163.5–167.6	90	1.17	0.85–1.60	323	1.47	1.24–1.75
≥167.7	96	1.33	0.96–1.84	254	1.40	1.16–1.69
Test for trend		p = 0.134			p < 0.001	

[1]Stratified by quintiles.–[2]Multivariate RRs were adjusted for study center, age, educational attainment, smoking status, alcohol consumption, parity, age at first pregnancy, age at menarche and current pill use.–[3]Multivariate RRs were adjusted for study center, age, educational attainment, smoking status, alcohol consumption, parity, age at first pregnancy, age at menarche and current HRT use.

TABLE IV – MULTIVARIATE-ADJUSTED RR OF BREAST CANCER BY ANTHROPOMETRIC MEASURES IN 73,542 PREMENOPAUSAL WOMEN, THE EPIC STUDY

Body measure[1]	Quintiles 1	2	3	4	5	p_{trend}
Weight (kg)	<56.8	56.8–61.9	62.0–67.4	67.5–74.9	≥75.0	
Number of cases	135	92	102	78	67	
RR (95% CI)[2]	Ref.	0.78 (0.60–1.03)	0.95 (0.74–1.25)	0.91 (0.68–1.22)	0.83 (0.61–1.13)	0.459
BMI (kg/m^2)	<21.6	21.6–23.5	23.6–25.6	25.7–28.7	≥28.8	
Number of cases	132	114	85	75	68	
RR (95% CI)[2]	Ref.	0.95 (0.73–1.23)	0.78 (0.59–1.04)	0.80 (0.59–1.09)	0.82 (0.59–1.14)	0.100
Waist circumference (cm)	<71.0	71.0–75.9	76.0–81.4	81.5–89.2	≥89.3	
Number of cases	130	139	65	74	66	
RR (95% CI)[2]	Ref.	1.30 (1.02–1.65)	0.78 (0.57–1.06)	1.00 (0.74–1.35)	1.07 (0.77–1.48)	0.631
RR (95% CI)[3]	Ref.	1.43 (1.11–1.84)	0.93 (0.67–1.31)	1.34 (0.92–1.94)	1.81 (1.11–2.97)	0.161
Hip circumference (cm)	<94.0	94.0–97.9	98.0–102.4	102.5–107.9	≥108.0	
Number of cases	120	101	89	96	68	
RR (95% CI)[2]	Ref.	0.99 (0.75–1.29)	0.92 (0.69–1.21)	1.07 (0.81–1.42)	0.97 (0.70–1.32)	0.957
RR (95% CI)[3]	Ref.	1.08 (0.82–1.43)	1.09 (0.80–1.48)	1.44 (1.02–2.02)	1.70 (1.05–2.77)	0.030
WHR (cm/cm)	<0.736	0.737–0.770	0.771–0.803	0.804–0.846	≥0.847	
Number of cases	136	106	85	86	61	
RR (95% CI)[2]	Ref.	0.86 (0.67–1.12)	0.83 (0.63–1.10)	0.98 (0.73–1.30)	0.92 (0.66–1.27)	0.731
RR (95% CI)[3]	Ref.	0.88 (0.68–1.14)	0.87 (0.66–1.16)	1.06 (0.79–1.43)	1.05 (0.74–1.50)	0.657

[1]Stratified by quintiles.–[2]Multivariate RRs were adjusted for study center, age, educational attainment, smoking status, alcohol consumption, parity, age at first pregnancy, age at menarche and current pill use.–[3]Further adjusted for BMI.

highest risk (RR = 1.47, CI 1.24–1.75) compared to short women (<156.0 cm). HRT did not modify the height–breast cancer association, and risk estimates were calculated for the total postmenopausal cohort, as presented in Table III.

On average, 23.5% of postmenopausal women used menopausal hormones at baseline. A statistically significant interaction was found between current HRT use and weight (p = 0.017), BMI (p = 0.003), waist circumference (p = 0.001) and hip circumference (p = 0.0005) but not WHR. Postmenopausal women who did not use hormones at baseline (76%) had elevated breast cancer risk with increasing weight ($p_{trend} < 0.0001$), BMI ($p_{trend} = 0.002$) and hip circumference ($p_{trend} = 0.002$) (Table VI). Weight at baseline was the strongest predictor, with a 65% increased risk for the highest quintile (≥75.0 kg) *vs.* the lowest quintile (<56.8 kg) among non-HRT users. The effect of weight on breast cancer risk was slightly attenuated after additional adjustment for height but remained statistically significant [RR by weight quintile 1.0, or 1.18 (95% CI 0.92–1.51), 1.26 (95% CI 0.99–1.60), 1.41 (95% CI 1.11–1.79), 1.50 (95% CI 1.18–1.91); $p_{trend} = 0.0003$]. Overweight (BMI = 25–30) and obese (BMI > 30) women had a 30% and 31% excess risk, respectively, compared to women with BMI < 25 ($p_{trend} = 0.001$). Among current HRT users, anthropometric measures tended to be inversely related to breast cancer. For example, obese women (BMI > 30) had a significant 34% reduced risk compared to lean women (BMI < 25) (Table VI). Further adjustment for duration of HRT use (available for 77% of current hormone users) did not materially alter these risk estimates, irrespective of the body measure examined (data not shown).

To assess further the overall effect of HRT use and BMI on breast cancer, we compared the risk of each combined BMI–HRT use category with a uniform reference category (BMI < 25.0, non-HRT user) (Fig. 1). Among nonusers, multivariate RRs were 1.28 (95% CI 1.11–1.48) for overweight women (BMI = 25.0–29.9) and 1.28 (95% CI 1.06–1.54) for obese women (BMI ≥ 30.0) compared to women in the normal weight range. In HRT users, irrespective of BMI status, breast cancer risk was higher than in nonusers. Yet, HRT users experienced a reduced risk with increasing BMI, or conversely, lean women had excess risk. The risk estimate for women in the normal weight range (BMI < 25.0) was 2.04 (95% CI 1.74–2.39). For overweight (BMI = 25–30) and obese (BMI ≥ 30.0) women, RRs were 1.93 (95% CI 1.58–2.35) and 1.39 (95% CI 0.95–2.03), respectively.

Neither waist circumference nor WHR, as a measure of central adiposity, was related to breast cancer risk in postmenopausal non-HRT users, whereas women in the top hip circumference quintile had a 56% increased risk (RR = 1.56, 95% CI 1.12–2.17) compared to women in the lowest quintile (Table VI). These BMI-adjusted risk estimates were not different from those when BMI was not accounted for (data not shown), except for waist circumference [RR by waist quintile = 1.0 or 1.04 (95% CI 0.81–1.33), 1.03 (95% CI 0.81–1.32), 1.21 (95% CI 0.96–1.53), 1.38 (95% CI 1.09–1.74); $p_{trend} = 0.0009$]. We repeated the analyses for each selected anthropometric measure, further adjusting for age at menopause (available for 84.5% of the postmenopausal cohort). Among non-HRT users, some point estimates (weight and BMI) were slightly attenuated but overall the results were not substantially altered (data not shown).

Country-specific and pooled analyses (Table V) showed that in the total group of postmenopausal women all country-specific RRs were greater than 1 and the pooled RR was 1.02 for continuous

TABLE V – COUNTRY-SPECIFIC AND POOLED MULTIVARIATE RR OF BREAST CANCER BY MENOPAUSAL STATUS FOR CONTINUOUS BODY MEASURES

Body measure	France: RR (95% CI)	Italy: RR (95% CI)	Spain:[1] RR (95% CI)	UK: RR (95% CI)	Netherlands: RR (95% CI)	Greece:[1] RR (95% CI)	Germany: RR (95% CI)	Sweden:[2] RR (95% CI)	Denmark: RR (95% CI)	Pooled:[3]RR (95% CI)	*P* (test for heterogeneity)
Height (cm)											
Premenopausal	1.02 (0.98–1.06)	1.02 (0.99–1.06)	1.02 (0.98–1.06)	0.98 (0.95–1.02)	1.05 (1.01–1.10)	1.02 (0.90–1.15)	1.00 (0.93–1.08)	—	1.04 (0.96–1.12)	1.01 (1.00–1.03)	0.53
Postmenopausal	1.02 (0.99–1.05)	1.04 (1.01–1.06)	1.05 (1.01–1.09)	1.01 (0.99–1.03)	1.02 (0.99–1.04)	1.06 (0.99–1.14)	1.03 (0.99–1.07)	1.03 (1.00–1.05)	1.01 (0.99–1.03)	1.02 (1.01–1.03)	0.54
Weight (kg)											
Premenopausal	1.01 (0.98–1.03)	1.00 (0.98–1.02)	1.00 (0.98–1.02)	0.99 (0.97–1.01)	1.01 (0.98–1.03)	0.99 (0.93–1.05)	0.99 (0.95–1.03)	—	0.99 (0.94–1.03)	1.00 (0.99–1.01)	0.93
Postmenopausal											
Non-HRT user	1.03 (1.02–1.05)	1.01 (0.99–1.03)	1.02 (1.00–1.04)	1.02 (1.01–1.03)	1.01 (0.99–1.02)	1.04 (1.00–1.07)	1.02 (1.00–1.04)	1.01 (0.99–1.02)	1.01 (0.99–1.02)	1.02 (1.01–1.02)	0.19
HRT user	0.99 (0.97–1.01)	1.01 (0.95–1.07)	—	1.00 (0.96–1.04)	1.00 (0.96–1.04)	—	1.00 (0.97–1.03)	1.00 (0.98–1.03)	1.00 (0.99–1.02)	1.00 (0.99–1.01)	0.98
BMI (kg/m^2)											
Premenopausal	0.99 (0.94–1.06)	0.97 (0.92–1.02)	0.99 (0.94–1.04)	0.97 (0.92–1.03)	0.98 (0.91–1.06)	0.96 (0.82–1.13)	0.98 (0.88–1.10)	—	0.91 (0.79–1.05)	0.98 (0.96–1.00)	0.97
Postmenopausal											
Non-HRT user	1.09 (1.04–1.14)	0.99 (0.95–1.04)	1.02 (0.97–1.07)	1.06 (1.03–1.09)	1.01 (0.97–1.05)	1.05 (0.99–1.13)	1.04 (0.98–1.10)	1.01 (0.97–1.05)	1.01 (0.97–1.05)	1.03 (1.01–1.05)	0.07
HRT user	0.96 (0.90–1.02)	1.04 (0.90–1.21)	—	0.99 (0.93–1.05)	0.95 (0.84–1.07)	—	0.97 (0.89–1.05)	0.99 (0.92–1.06)	1.01 (0.96–1.06)	0.99 (0.96–1.01)	0.79
Waist circumference (cm)[4]											
Premenopausal	1.01 (0.97–1.05)	0.99 (0.95–1.04)	1.02 (0.98–1.06)	1.02 (0.98–1.06)	1.05 (0.99–1.10)	0.94 (0.83–1.07)	1.02 (0.96–1.08)	—	1.01 (0.92–1.11)	1.01 (0.99–1.03)	0.71
Postmenopausal											
Non-HRT user	1.00 (0.97–1.03)	1.01 (0.98–1.04)	1.04 (1.00–1.08)	1.01 (0.99–1.04)	1.03 (1.00–1.06)	0.99 (0.95–1.04)	1.00 (0.95–1.05)	1.01 (0.98–1.04)	0.99 (0.95–1.02)	1.01 (1.00–1.02)	0.51
HRT user	1.02 (0.98–1.06)	0.97 (0.88–1.06)	—	0.99 (0.95–1.03)	1.03 (0.95–1.12)	—	0.97 (0.92–1.03)	1.06 (1.01–1.10)	0.96 (0.92–0.99)	1.00 (0.97–1.03)	0.03
Hip circumference (cm)[4]											
Premenopausal	1.04 (0.99–1.08)	1.03 (0.99–1.08)	1.01 (0.97–1.06)	1.03 (0.98–1.07)	1.07 (1.00–1.15)	0.98 (0.85–1.13)	1.05 (0.94–1.17)	—	0.99 (0.89–1.12)	1.02 (1.01–1.05)	0.81
Postmenopausal											
Non-HRT user	1.05 (1.01–1.10)	1.01 (0.97–1.05)	1.05 (1.00–1.11)	1.02 (0.99–1.06)	1.03 (0.99–1.07)	1.03 (0.96–1.11)	1.05 (0.98–1.11)	1.02 (0.99–1.06)	1.04 (0.99–1.08)	1.03 (1.01–1.04)	0.88
HRT user	0.99 (0.95–1.03)	0.97 (0.87–1.08)	—	1.02 (0.97–1.07)	0.99 (0.90–1.10)	—	1.03 (0.96–1.11)	1.01 (0.95–1.06)	0.99 (0.96–1.04)	1.00 (0.98–1.02)	0.96
WHR (cm/cm)[4,5]											
Premenopausal	0.99 (0.95–1.03)	0.98 (0.94–1.02)	1.01 (0.97–1.05)	1.00 (0.96–1.04)	1.01 (0.96–1.07)	0.95 (0.84–1.08)	1.00 (0.93–1.08)	—	1.01 (0.93–1.10)	0.99 (0.98–1.01)	0.85
Postmenopausal											
Non-HRT user	0.96 (0.92–1.00)	1.01 (0.98–1.03)	1.01 (0.97–1.05)	1.00 (0.97–1.03)	1.02 (0.99–1.05)	0.97 (0.91–1.03)	0.98 (0.93–1.02)	0.99 (0.97–1.03)	0.97 (0.95–1.00)	0.99 (0.98–1.01)	0.33
HRT user	1.02 (0.99–1.04)	0.98 (0.88–1.09)	—	0.98 (0.94–1.03)	1.03 (0.95–1.12)	—	0.96 (0.91–1.01)	1.06 (1.01–1.10)	0.97 (0.94–0.99)	1.00 (0.97–1.03)	0.01

[1]Risk estimates for postmenopausal HRT users not presented due to low number of cases ($n \leq 5$).–[2]Data on premenopausal women not available.–[3]Multivariate RRs were adjusted for age, educational attainment, smoking status, alcohol consumption, parity, age at first pregnancy, age at menarche and current pill use (premenopausal).–[4]Waist circumference, hip circumference and WHR were further adjusted for BMI.–[5]WHR was multiplied by 100 for this analysis; risk estimates are presented for 0.01 unit change in WHR.

TABLE VI – MULTIVARIATE-ADJUSTED RR OF BREAST CANCER BY ANTHROPOMETRIC MEASURES STRATIFIED BY CURRENT HRT USE IN 103,344 POSTMENOPAUSAL WOMEN, THE EPIC STUDY

Body measure[1]	Non-HRT user (n = 79,030)			HRT user (n = 24,314)		
	Cases	RR	CI	Cases	RR	CI
Weight (kg)[2]						
<56.8	117	Reference		104	Reference	
56.8–61.9	147	1.21	0.95–1.55	109	1.20	0.91–1.58
62.0–67.4	183	1.33	1.05–1.68	128	1.29	0.98–1.69
67.5–74.9	216	1.51	1.20–1.91	89	1.04	0.77–1.40
≥75.0	248	1.65	1.32–2.08	64	0.92	0.66–1.28
Test for trend		$p < 0.0001$			$p = 0.529$	
BMI (kg/m^2) quintiles[2]						
<21.6	98	Reference		122	Reference	
21.6–23.5	127	1.02	0.78–1.33	116	0.90	0.69–1.17
23.6–25.6	206	1.35	1.06–1.73	113	0.91	0.70–1.19
25.7–28.7	241	1.38	1.08–1.76	92	0.85	0.64–1.13
≥28.8	239	1.36	1.06–1.75	51	0.71	0.50–1.01
Test for trend		$p = 0.002$			$p = 0.073$	
BMI (kg/m^2) classification[2]						
<25.0	350	Reference		319	Reference	
25.0–29.9	380	1.30	1.12–1.51	145	0.94	0.76–1.15
>30.0	181	1.31	1.08–1.59	30	0.66	0.45–0.98
Test for trend		$p = 0.0012$			$p = 0.064$	
Waist circumference (cm)[3]						
<71.0	114	Reference		134	Reference	
71.0–75.9	141	1.01	0.78–1.30	112	0.89	0.68–1.16
76.0–81.4	158	0.98	0.76–1.27	103	0.88	0.65–1.18
81.5–89.2	230	1.12	0.86–1.46	94	0.81	0.57–1.16
>89.2	268	1.21	0.87–1.67	51	0.68	0.41–1.12
Test for trend		$p = 0.192$			$p = 0.169$	
Hip circumference (cm)[3]						
<94.0	133	Reference		130	Reference	
94.0–98.0	133	1.04	0.81–1.34	121	1.19	0.91–1.56
99.0–102.4	178	1.31	1.02–1.67	106	1.15	0.85–1.55
102.5–108.0	228	1.39	1.07–1.80	83	0.96	0.67–1.38
>108.0	239	1.56	1.12–2.17	54	1.02	0.61–1.69
Test for trend		$p = 0.002$			$p = 0.873$	
WHR (cm/cm)[3]						
<0.736	116	Reference		100	Reference	
0.737–0.770	148	0.92	0.72–1.18	120	0.95	0.72–1.25
0.771–0.803	183	0.91	0.72–1.16	110	0.93	0.70–1.23
0.804–0.846	215	0.91	0.72–1.15	95	0.85	0.63–1.15
>0.846	249	0.94	0.74–1.21	69	0.85	0.60–1.20
Test for trend		$p = 0.740$			$p = 0.250$	

[1]Stratified by quintiles.–[2]Multivariate RRs were adjusted for study center, age, educational attainment, smoking status, alcohol consumption, parity, age at first pregnancy and age at menarche.–[3]Further adjusted for BMI.

height (per 1 cm increase). Among non-HRT users, both weight and BMI were positively associated with breast cancer in all countries, except Italy (for weight only). For one increment of weight (1 kg) or BMI (1 kg/m^2), pooled RRs were 1.02 and 1.03, respectively. Hip circumference was positively associated with breast cancer in non-HRT users (pooled RR = 1.03 per 1 cm increase). No evidence of heterogeneity between countries was present for any of the selected body measures, except for waist circumference and WHR among HRT users.

DISCUSSION

In this large prospective cohort study of 176,886 European women, aged 18–80 years at baseline, body size, assessed by various anthropometric measures, was more strongly associated with breast cancer risk in postmenopausal than premenopausal women. Height was positively associated with breast cancer in the entire cohort but was a significant predictor only among postmenopausal women. HRT use modified the relation between body weight, BMI, waist and hip circumferences and postmenopausal breast cancer incidence, such that the increased risk was observed only among non-HRT users. Among women who used HRT at baseline, body size tended to be inversely related to breast cancer risk. Hip circumference, in contrast to both waist circumference and WHR, was associated with elevated risk among postmenopausal women, while among premenopausal women waist and hip circumferences were associated with excess risk only after adjustment for BMI.

The major strength of this large, multicenter study is that all body measures assessed at baseline were direct, in contrast to the self-reported data used in the majority of previous studies. Thus, potential bias, *i.e.,* attenuation of risk estimates because of imperfect measurements, should be minimal. Furthermore, the analysis combined data from several European cohorts with profound cultural differences.

Our results indicate that tall stature is associated with increased breast cancer risk, although the magnitude of the association was weaker in pre- than in postmenopausal women, confirming previous evidence.[2,26] Pooled risk estimates were higher, specifically for postmenopausal women (10% per height increase of 5 cm), than those reported in the Pooling Project (7% per increment of 5 cm).[26] The underlying mechanisms for the association between height and breast cancer risk are not fully understood. The relation may be explained by factors jointly influencing the development of both height, *i.e.,* bone growth, and breast cancer. Suggested factors include prenatal and childhood exposures, such as birth weight, diet and infection, as well as energy balance and insulin-like growth factors.[3,7,37,38]

Among premenopausal women, weight and BMI were inversely, though nonsignificantly, associated with breast cancer

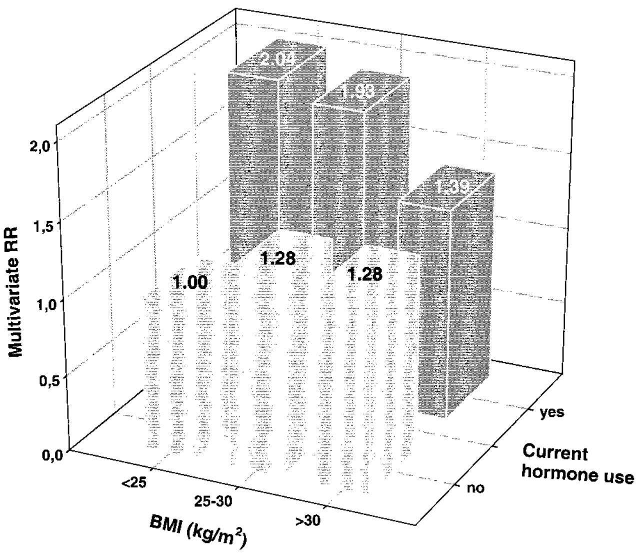

FIGURE 1 – Multivariate adjusted RR of breast cancer by BMI category and current hormone use among postmenopausal women (n = 103,344), the EPIC study.

risk. This is in agreement with earlier investigations.[2,26,39,40] Among postmenopausal women the relation between weight and BMI differed according to current HRT use. Thus, the lack of an overall strong association of BMI and postmenopausal breast cancer in our study was partly explained by current HRT use. This observation is in line with results from the WHI observation study,[14] the Pooling Project[26] and an earlier report from the NHS,[24] all indicating a stronger BMI–breast cancer association in non-HRT users. A similar finding was also described in the Swedish cohort from Malmö included in this analysis, using a more precise measure of body fatness (% body fat, bioelectrical impedance) than BMI.[41]

Examination of the modifying effect using a common reference group (non-HRT users with BMI < 25) showed that the increase in risk by adiposity was confined to women who were not using hormones, while among HRT users the risk was much more pronounced for women of low BMI than for those of high BMI, a finding also reported by others.[20,23] Our results support the estrogen excess hypothesis as an underlying mechanism for postmenopausal breast cancer, relating observations on body weight to endogenous levels of estrogens.

The magnitude of the usually observed moderate BMI–breast cancer association should be increased when the potentially confounding effect of exogenous hormones is removed. However, in our data among non-HRT users, the RR was only moderately increased by 36% in women in the top quintile (BMI $\geq$ 28.8). The risk did not increase beyond BMI of approximately 29 kg/m^2 (using quintiles or categories), which contrasts with results from the WHI observation study, the only other prospective study that has relied on both measured anthropometric data and classification by use of postmenopausal hormones. Risk estimates for the 2 upper quintiles (BMI = 27.4–31.1, BMI $>$31.1) among never-users were RR = 1.70 (95% CI 1.08–2.69) and RR = 2.52 (95% CI 1.62–3.93), respectively.[14] Obviously, the American women included in that study were more obese than EPIC participants. Notably, data from the Pooling Project, adjusting for postmenopausal HRT use, also indicated that the RR did not increase further above BMI of more than 28 kg/m.[2,26] It has been suggested that the absence of an increase in risk beyond this BMI level may be due to the residual effect of the lower risk for breast cancer observed among obese premenopausal women: obese postmenopausal women are likely to be overweight before menopause and, therefore, may have only a moderately increased breast cancer risk because of the reduced risk experienced during their premenopausal life.[18,24]

The pooled estimates in the present study indicate a 2% reduction (nonsignificant) in risk per unit of increase in BMI (1 kg/m^2) among premenopausal and a 3% increase in risk among postmenopausal non-HRT users, corroborating the multivariate adjusted estimates from recent meta-analyses.[18,42] Yet, the risk estimates for both BMI (13% per 4 kg/m^2 increase) and weight (22% per 10 kg increase) among postmenopausal women in our study are higher than those reported from the Pooling Project[26] and may be due to the HRT stratification applied in our analysis.

WHR was not significantly related to pre- or postmenopausal breast cancer risk, confirming some, but not all, previous reports from prospective studies.[14,25,39,43–47] This finding may contribute to the current debate about the role of abdominal adiposity and breast cancer occurrence, specifically in postmenopausal women. Methodologic issues may explain some of the discrepant results. The WHI observation study, with both measured anthropometric data and stratification for HRT user status, also showed no effect of WHR.[14] In contrast, high WHR was strongly associated with increased risk among never-users of postmenopausal hormones in the NHS,[25] which relied on self-reported anthropometric data and had a slightly longer follow-up of about 8 years.

Waist circumference was moderately associated with postmenopausal, but not with premenopausal, breast cancer. After controlling for BMI, the association became more positive in premenopausal women and was attenuated in postmenopausal women, probably due to the fact that BMI was inversely associated with premenopausal breast cancer and positively associated with postmenopausal breast cancer. A similar finding was reported from the NHS[25] and for postmenopausal HRT never-users in the WHI observation study.[14]

Interestingly, among the measures of fat distribution examined in this study, hip circumference was a strong predictor of postmenopausal breast cancer among non-HRT users, with or without adjustment for BMI. In HRT never-users of the WHI observation study, increasing hip circumference was also associated with elevated risk (highest *vs.* lowest quintile RR = 2.43, 95% CI 1.58–3.73) but not significantly associated with breast cancer when controlling for BMI.[14] In other prospective studies that did not stratify by HRT use, hip circumference was positively, though not significantly, associated with postmenopausal breast cancer.[25,39] Concerning premenopausal women, a positive and significant trend between hip circumference and breast cancer risk became apparent only after adjustment for BMI in our study, contrasting results from the NHS that indicated an inverse association in premenopausal women irrespective of statistical adjustments.[25] The positive association observed in our data may be due to the same phenomenon as seen with waist circumference when controlling for BMI.

Possible limitations of our study warrant consideration before interpretation of the findings. Our conclusions are based on results derived from a very large cohort (cases n = 1,879) but with a limited duration of follow-up (4.7 years). Reexamination of our data after removal of preexisting disease by excluding individuals censored during the first year of follow-up, however, did not materially change the main findings (data not shown).

It cannot be ruled out that some confounding bias is still present, due to the lack of inclusion of other potential risk factors, such as family history of breast cancer or dietary intake. Data on family history were not available, and inclusion of energy intake and percentage energy from fat as cofactors (data not shown) did not affect the risk estimates of any of the body measures; these cofactors were omitted from the main analysis. Body circumferences, which served as indicators of central adiposity, were differently measured in the participating EPIC study centers.[32] We formally tested whether the different measurement methods influenced the results (data not shown). No effect was observed.

Age at diagnosis modified the generally modest BMI–breast cancer association among postmenopausal women in some prospective studies,[26,40] where the higher risk of breast cancer in relation to BMI was mainly confined to women aged 65 years and older at breast cancer diagnosis. In contrast, Morimoto *et al.*[14] described the opposite effect; *i.e.,* the risk was much greater in younger women aged 50–59 years compared to those aged 70–79 years. In the present study, there was no indication of an effect modification by age at diagnosis (data not shown), thus not supporting any of the earlier directional findings.

In our analysis with postmenopausal women, we used "current" instead of "ever" use of hormones for stratification, expecting a stronger impact of recent use of HRT than distant use, as reported by others.[20] When using ever use (data not shown), the direction of the associations was unchanged in the strata. Risk estimates were slightly attenuated for some body measures, but overall results were not affected.

In conclusion, in this European prospective cohort study, general obesity appeared to be more strongly associated with postmenopausal breast cancer risk than abdominal obesity assessed by waist circumference or WHR, specifically in women not using exogenous hormones. Notably, hip circumference was a strong predictor of breast cancer, after adjusting for BMI, in both pre- and postmenopausal women, which may suggest a different role of this body measure in breast cancer etiology and merits further exploration. Overweight is one of the few modifiable breast cancer risk factors and, thus, an important measure for breast cancer prevention and prognosis.

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