ORIGINAL ARTICLE

Several anthropometric measurements and breast cancer risk: results of the E3N cohort study

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Objective: To investigate the association between various anthropometric characteristics and breast cancer.
Design: Longitudinal prospective cohort study. Follow-up between 1995 and 2000.
Subjects: In total, 69 116 women (age: 45–70 years; mean follow-up: 3.6 years), 275 premenopausal and 860 postmenopausal incident invasive breast cancers.
Measurements: Self-reported height, weight, breast, thorax, waist and hip circumferences and calculated body mass index (BMI) and waist-to-hip ratio (WHR) at baseline.
Results: A slight increase in risk with increasing height was found. Weight, BMI, thorax and waist circumferences and WHR were negatively related to breast cancer risk among premenopausal women. The relationships became non significant after additional adjustment for BMI. An increased risk of premenopausal breast cancer with an android body shape (WHR > 0.87) might possibly be confined to obese women. Among postmenopausal women, all anthropometric measurements of corpulence were positively associated with breast cancer risk but became non significant after additional adjustment for BMI. No difference in risk of postmenopausal breast cancer according to HRT use was observed.
Conclusion: The study confirmed that adiposity was negatively associated to premenopausal breast cancer risk and positively associated to postmenopausal breast cancer risk. Further studies will be needed to specify clearly the association between WHR and breast cancer risk, particularly before menopause.
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Introduction

Many studies [1–4] have investigated the relationship between anthropometric characteristics, particularly height, weight and body mass index (BMI) and breast cancer risk throughout a woman's life. Most suggest that taller women are at increased risk of breast cancer irrespective of menopausal status. Weight and BMI, as markers of fat deposition, are associated with a decrease in breast cancer risk before menopause and with an increase after. Whereas most cohort studies show lower risks of premenopausal breast cancer among overweight or obese women, the results of case–control studies are contradictory, with negative, null or positive associations.[2,3] Case–control studies are in better agreement about an increase in risk of postmenopausal breast cancer with overweight and obesity, but the results of cohort studies are less consistent.[2–4] It has been hypothesized that abdominal fat, assessed by waist circumference and waist-to-hip ratio (WHR), may be better correlated to the metabolic mechanisms of obesity involved in breast carcinogenesis.[5] However, most studies on these indices [4] have produced conflicting results and although abdominal obesity is likely to be positively related to postmenopausal breast cancer, it seems not to be predictive of premenopausal breast cancer risk. In a recent meta-analysis,[6] an increase in breast cancer risk was associated with abdominal obesity, assessed by WHR, irrespective of menopausal status.

As obesity influences metabolic and hormonal mechanisms and is also increasingly prevalent in Western societies, there is a need for examining variables such as height, weight, thorax, breast, hip and waist circumferences and indices such as BMI and WHR, capable of characterizing obesity in relation to pre- and postmenopausal breast cancer occurrence.

The E3N (Etude Epidémiologique de femmes de la Mutuelle Générale de l'Education Nationale) prospective cohort study on French women offered the opportunity to

examine the potential relation between pre- and postmeno-pausal breast cancer occurrence over a 5-year follow-up period and these anthropometric variables, reported at the start of follow-up.

Material and methods

E3N is a prospective cohort study conducted in France. [7] Its main objective is to investigate risk factors for cancer. The cohort consists of 98 997 women living in France and insured with the Mutuelle Générale de l'Education Nationale (MGEN), a national health insurance scheme primarily covering teachers. They were aged 40–65 years at inclusion (between June 1990 and November 1991) and were enrolled after replying to a baseline questionnaire. Part of the E3N cohort, that is, women who replied to the dietary questionnaire sent out in 1993, is also included in the European Prospective Investigation on Cancer (EPIC).

Participants were followed up at 24-month intervals by a self-administered questionnaire. The present study is based on the data collected in the fourth questionnaire (1995), where women were asked to report their height, weight, thorax, breast, waist and hip circumferences. More than two-thirds ($n = 69 150$) of the participants initially included in the cohort answered this questionnaire. Women were asked to measure their anthropometric circumferences with a measuring tape. Weight and height were measured wearing no shoes, in underwear. Breast circumference was measured at nipples, thorax circumference at the base of the breast, waist circumference at the narrowest torso circumference and hip circumference at the widest. BMI and WHR were calculated on the basis of these self-reported measurements.

Menopausal status was recorded in each follow-up ques-tionnaire. To ensure that variables were as accurate as possible with regard to menopause, the whole set of answers on date and type of menopause (natural or induced by bilateral oophorectomy, chemotherapy, radiotherapy or other treatment), date of last menstruation, date of start of menopausal symptoms and date of hysterectomy, where appropriate, were taken into account. Postmenopause was defined as the cessation of periods for natural reasons or due to radiation, chemotherapy or surgery (total oophorectomy). In part of the analysis, participants were classified into two subgroups defined by their menopausal status in 1995. Women with undefined menopausal status (for instance because of continuous use of hormonal treatments or hysterectomy with no additional information on oophor-ectomy) and those who had never menstruated ($n = 4$) were not considered in the subgroup analysis. Women who had reported a cancer other than a basal cell carcinoma at enrolment were also excluded. The mean follow-up time was 3.6 years (standard deviation (s.d.) = 1.7 years) for the premenopausal subgroup and 4.7 years (s.d. = 0.9 year) for the postmenopausal subgroup.

All questionnaires asked participants whether breast cancer had been diagnosed, requesting the address of their physician and permission to contact him or her. Deaths in the cohort were detected from reports by family members or the postal service and by searching the insurance company (MGEN) database, which contains information on vital status. Information on cause of death was obtained from the National Service on Causes of Deaths (CepiDC, INSERM).

In the case of nonrespondents, information on the reimbursement of hospital fees was obtained from the MGEN database. Diagnostic information was then sought from the hospital physician, making it possible to find additional breast cancer cases.

The present analysis is based on the follow-up of a total sample of 69 116 women, 1135 of whom developed breast cancer (275 premenopausal and 860 postmenopausal) dur-ing follow-up.

The adjustment variables taken into account were history of breast cancer in first-degree relatives (yes/no), age at menarche (cut points: 12, 13, 14), age at first birth (cut points: 23, 26, 30), parity (0, 1–3, $\geqslant 4$), history of benign breast disease (yes/no), alcohol consumption (0, $\leqslant 1$, >1 drinks per week), number of years of education (0, 1–5, 6–9, 10–13, 14–15, $\geqslant 16$), marital status (ever married/never married) and physical activity (quartiles of weekly energy expenditure expressed in MET-hour/week Additional adjust-ments were made for BMI in specific analyses. Data were analysed using Cox proportional hazards models with age as the time scale.[8] Anthropometric factors were considered as continuous variables and categorized into quartiles. For BMI, WHO cut points[9] were also considered.

All analyses were performed with SAS® Software.

Results

Correlations between anthropometric measurements are presented in Table 1. Correlations were similar between pre- and postmenopausal women. The highest correlations were between BMI and breast circumference (at nipples) and between BMI and waist circumference. The lowest correla-tions were between WHR and BMI.

Characteristics reported in the fourth questionnaire (1995) were compared in cases and noncases (Table 2). Both pre- and postmenopausal breast cancer cases were significantly older at first full-term pregnancy and more often had a family history of breast cancer and a personal history of benign breast disease than noncases. Postmenopausal breast cancer cases also were significantly older at menopause and had fewer children.

Whatever the menopausal status, no difference in height was observed between cases and noncases. Premenopausal breast cancer cases had a significantly lower weight (58.3 kg versus 59.8 kg, $P < 0.05$), BMI (22.2 kg/m^2 versus 22.7 kg/m^2, $P < 0.01$), thorax circumference (79 cm versus 81.2 cm, $P < 0.01$) and breast circumference (90.9 cm versus 91.8 cm,

Table 1 Correlation matrix of various anthropometric characteristics self-reported in the fourth follow-up questionnaire[a], by menopausal status. E3N cohort

Variable	Thorax circumference	Breast circumference at nipples	Waist circumference	Hip circumference	WHR	BMI
Premenopausal women (n = 20063)						
Thorax circumference (cm)	1.00					
Breast circumference at nipples (cm)	0.30[b]	1.00				
Waist circumference (cm)	0.25[b]	0.38[b]	1.00			
Hip circumference (cm)	0.16[b]	0.27[b]	0.24[b]	1.00		
WHR	0.03[b]	0.04[b]	0.30[b]	−0.14[b]	1.00	
BMI (kg/m^2)	0.35[b]	0.58[b]	0.52[b]	0.42[b]	0.04[b]	1.00
Postmenopausal women (n = 41680)						
Thorax circumference (cm)	1.00					
Breast circumference at nipples (cm)	0.42[b]	1.00				
Waist circumference (cm)	0.37[b]	0.35[b]	1.00			
Hip circumference (cm)	0.24[b]	0.21[b]	0.21[b]	1.00		
WHR	0.04[b]	0.07[b]	0.27[b]	−0.09[b]	1.00	
BMI (kg/m^2)	0.56[b]	0.52[b]	0.50[b]	0.36[b]	0.04[b]	1.00

[a]Sent in 1995. [b]Correlation significantly different from zero, *P*-value $\leqslant 10^{-4}$.

Table 2 Comparison of general characteristics between breast cancer cases and noncases, by menopausal status. E3N cohort

Variable	Cases mean (s.d.) or %	Noncases mean (s.d.) or %	P-value[a]
Premenopausal women			
	(n = 275)	(n = 20564)	
Age at fourth questionnaire (years)	43.4 (2.5)	43.1 (2.1)	$\leqslant$0.05
Age at menarche (years)	12.6 (1.3)	12.7 (1.4)	NS
Age at first birth (years)	25.2 (4.6)	24.5 (4.1)	$\leqslant$0.01
Number of full-term pregnancies	1.9 (1.0)	1.9 (1.1)	NS
Years of education	14.1 (2.3)	13.9 (2.5)	NS
Alcohol consumption[b] (g/day)	10.1 (13.7)	10.8 (14.2)	NS
Ever married	84.2%	84.6%	NS
Oral contraceptive use[c]	63.3%	61.0%	NS
History of benign breast disease[c]	49.8%	37.2%	$\leqslant$0.0001
Family history of breast cancer in first-degree relatives[c]	15.3%	10.7%	$\leqslant$0.01
Postmenopausal women			
	(n = 860)	(n = 41497)	
Age at fourth questionnaire (years)	52.5 (5.5)	52.5 (6.1)	NS
Age at menarche (years)	12.7 (1.5)	12.8 (1.5)	NS
Age at first birth (years)	24.9 (4.3)	24.4 (4.0)	$\leqslant$0.01
Age at menopause (years)	49.8 (4.1)	48.9 (4.4)	$\leqslant$0.0001
Number of full-term pregnancies	1.9 (1.2)	2.0 (1.3)	$\leqslant$0.001
Years of education	13.2 (3.1)	13.2 (2.9)	NS
Alcohol consumption[b] (g/day)	10.9 (15.7)	10.7 (14.0)	NS
Ever married	82.4%	80.1%	NS
Oral contraceptive use[c]	30.0%	31.4%	NS
History of benign breast disease[c]	45.4%	30.8%	$\leqslant$0.0001
Family history of breast cancer in first-degree relatives[c]	18.0%	11.9%	$\leqslant$0.0001

[a]Calculated by *t*-tests and χ^2 tests. [b]Recorded in the dietary questionnaire (1993). [c]Before the fourth questionnaire (1995).

P < 0.05) than noncases. No significant differences were observed in the postmenopausal subgroup between cases and noncases (Table 3).

Table 3 Comparison of various anthropometric characteristics obtained from the fourth questionnaire between breast cancer cases and noncases, by menopausal status. E3N cohort

Variable	Cases mean (s.d.)	Noncases mean (s.d.)	P-value[a]
Premenopausal women			
	(n = 275)	(n = 20564)	
Height (cm)	162.2 (5.8)	162.2 (5.6)	NS
Weight (kg)	58.3 (8.5)	59.8 (9.5)	$\leqslant$0.05
BMI (kg/m^2)	22.2 (2.8)	22.7 (3.3)	$\leqslant$0.01
Thorax circ. (cm)	79.0 (5.8)	81.2 (13.0)	$\leqslant$0.01
Breast circ. at nipples (cm)	90.9 (6.6)	91.8 (10.0)	$\leqslant$0.05
Waist circ. (cm)	76.2 (9.8)	74.6 (11.8)	NS
Hip circ. (cm)	95.8 (21.6)	95.8 (16.6)	NS
WHR	0.81 (0.44)	0.79 (0.34)	NS
Postmenopausal women			
	(n = 860)	(n = 41497)	
Height (cm)	161.5 (5.7)	161.2 (5.7)	NS
Weight (kg)	61.5 (9.6)	60.9 (9.8)	NS
BMI (kg/m^2)	23.6 (3.5)	23.5 (3.5)	NS
Thorax circ. (cm)	81.7 (7.4)	81.4 (9.8)	NS
Breast circ. at nipples (cm)	93.8 (8.2)	93.6 (12.1)	NS
Waist circ. (cm)	77.3 (9.1)	77.2 (15.3)	NS
Hip circ. (cm)	97.9 (9.1)	98.0 (19.7)	NS
WHR	0.79 (0.1)	0.80 (0.5)	NS

[a]Calculated by *t*-tests.

RRs of breast cancer associated with anthropometric variables are presented in Table 4. Among *premenopausal* women, the risk was greater, though not significantly, in the three upper quartiles of height than in the lowest. Weight and BMI were inversely related to premenopausal breast cancer risk, with significant negative trends (both *P* for trend <0.05) and RRs of 0.57 (0.42–0.98) and 0.61 (0.42–0.89), respectively, for the fourth quartiles of weight and BMI compared with the first quartiles. Using the WHO categorization of BMI, we observed an RR of 0.26 (0.06–1.00) when comparing women with a BMI greater than 30 kg/m^2 with women with a BMI between 18.5 and 25 kg/m^2. However, this estimate was based on only two cases.

Variable	Total	Cases	Multivariate[a] RRs	P for trend[b]	BMI adjusted RRs	P for trend		Total	Cases	Multivariate[a] RRs	P for trend	BMI adjusted RRs	P for trend
Premenopausal women							**Postmenopausal women**						
Height (cm)													
Q1 <158	4088	(49)	1.00 (reference)				Q1 <158	11316	(352)	1.00 (reference)			
Q2 [158-162[	5447	(81)	1.46 (0.97–2.19)	NS			Q2 [158–161[	9740	(330)	1.07 (0.86–1.34)	NS		
Q3 [162–166[	5648	(69)	1.13 (0.73–1.74)				Q3 [161–165[	9770	(316)	0.88 (0.69–1.13)			
Q4⩾166	5656	(76)	1.26 (0.80–1.98)				Q4⩾165	12079	(470)	1.06 (0.83–1.34)			
Weight (kg)													
Q1 <54	6006	(74)	1.00 (reference)				Q1 <54	10813	(243)	1.00 (reference)			
Q2 [54–59[	5042	(58)	0.73 (0.50–1.07)	⩽0.05			Q2 [54–60[	12244	(340)	1.18 (0.93–1.49)	NS		
Q3 [59–65[	4655	(44)	0.76 (0.51–1.11)				Q3 [60–66[	8851	(218)	1.10 (0.86–1.40)			
Q4⩾65	4297	(36)	0.57 (0.42–0.98)				Q4⩾66	9949	(272)	1.23 (0.97–1.57)			
BMI (kg/m²)													
Q1 <20.7	5458	(67)	1.00 (reference)				Q1 <20.0	10507	(244)	1.00 (reference)			
Q2 [20.7–22.3[	5196	(52)	0.72 (0.49–1.08)	⩽0.05			Q2 [20.0–22.8[	10451	(259)	1.16 (0.91–1.48)	NS		
Q3 [22.3–24.4[	4706	(53)	0.87 (0.60–1.25)				Q3 [22.8–25.1[	10439	(249)	1.10 (0.87–1.40)			
Q4⩾24.4	4640	(40)	0.61 (0.42–0.89)				Q4⩾25.1	10460	(285)	1.21 (0.96–1.52)			
BMI (kg/m²)													
< 18.5	401	(13)	1.15 (0.47–2.79)				< 18.5	1304	(21)	0.49 (0.22–1.10)			
[18.5–25[	15599	(170)	1.00 (reference)	c			[18.5–25[	29440	(714)	1.00 (reference)	c		
[25–30[	2954	(27)	0.84 (0.56–1.27)				[25–30[	9039	(244)	1.07 (0.89–1.30)			
⩾30	695	(2)	0.26 (0.06–1.00)				⩾30	2074	(58)	1.44 (1.04–1.99)			
Thorax circ. (cm)													
Q1 <76	4725	(61)	1.00 (reference)		1.00 (reference)		Q1 <76	8394	(205)	1.00 (reference)		1.00 (reference)	
Q2 [76–80[	5177	(69)	1.06 (0.75–1.49)	⩽0.05	1.08 (0.76–1.54)	NS	Q2 [76–80[	9218	(205)	0.96 (0.75–1.22)	⩽0.05	0.96 (0.74–1.23)	NS
Q3 [80–84[	5036	(45)	0.71 (0.48–1.05)		0.74 (0.49–1.13)		Q3 [80–85[	11907	(326)	1.24 (1.00–1.55)		1.17 (0.92–1.48)	
Q4⩾84	4916	(43)	0.70 (0.47–1.03)		0.82 (0.50–1.36)		Q4⩾85	12042	(317)	1.16 (0.92–1.45)		1.01 (0.76–1.35)	
Breast circ. (cm)													
Q1 <87	4842	(56)	1.00 (reference)		1.00 (reference)		Q1 <88	9046	(230)	1.00 (reference)		1.00 (reference)	
Q2 [87–91[	5203	(60)	0.98 (0.68–1.42)	⩽0.05	1.06 (0.72–1.54)	NS	Q2 [88–92[	9454	(223)	1.04 (0.82–1.31)	NS	1.01 (0.79–1.28)	NS
Q3 [91–96[	5169	(64)	1.08 (0.75–1.55)		1.14 (0.76–1.72)		Q3 [92–98[	12161	(313)	1.10 (0.89–1.37)		1.00 (0.79–1.28)	
Q4⩾96	4758	(38)	0.68 (0.45–1.03)		0.89 (0.51–1.55)		Q4⩾98	10977	(287)	1.16 (0.93–1.45)		0.99 (0.73–1.35)	
Waist circ. (cm)													
Q1 <69	4666	(60)	1.00 (reference)		1.00 (reference)		Q1 <70	8125	(178)	1.00 (reference)		1.00 (reference)	
Q2 [69–74[	5737	(64)	0.87 (0.61–1.24)	⩽0.05	0.83 (0.58–1.21)	NS	Q2 [70–75[	10676	(269)	1.21 (0.95–1.53)	⩽0.05	1.17 (0.91–1.49)	NS
Q3 [74–79[	4607	(56)	0.97 (0.68–1.40)		0.98 (0.65–1.48)		Q3 [75–81[	11214	(302)	1.32 (1.04–1.66)		1.21 (0.94–1.56)	
Q4⩾79	5028	(37)	0.58 (0.38–0.88)		0.66 (0.38–1.15)		Q4⩾81	11977	(323)	1.21 (0.95–1.54)		1.01 (0.73–1.39)	
Hip circ. (cm)													
Q1 <90	4206	(47)	1.00 (reference)		1.00 (reference)		Q1 <92	9551	(218)	1.00 (reference)		1.00 (reference)	
Q2 [90–95[	5493	(61)	1.00 (0.68–1.46)	NS	1.16 (0.78–1.72)	NS	Q2 [92–96[	8913	(229)	1.16 (0.92–1.47)	NS	1.12 (0.88–1.43)	NS
Q3 [95–100[	4838	(58)	1.10 (0.75–1.62)		1.29 (0.84–1.98)		Q3 [96–102[	11792	(297)	1.17 (0.94–1.47)		1.07 (0.84–1.37)	
Q4⩾100	5481	(52)	0.88 (0.43–1.31)		1.35 (0.79–2.32)		Q4⩾102	11733	(327)	1.20 (0.96–1.50)		1.01 (0.75–1.37)	
WHR													
Q1 <0.74	4716	(58)	1.00 (reference)		1.00 (reference)		Q1 <0.75	10291	(249)	1.00 (reference)		1.00 (reference)	
Q2 [0.74–0.78[	5648	(70)	0.99 (0.70–1.41)	NS	1.05 (0.73–1.49)	NS	Q2 [0.75–0.78[	9033	(241)	1.09 (0.87–1.37)	NS	1.10 (0.88–1.39)	NS
Q3 [0.78–0.82[	5141	(56)	0.88 (0.60–1.25)		0.87 (0.59–1.27)		Q3 [0.78–0.82[	11444	(310)	1.12 (0.90–1.38)		1.08 (0.87–1.35)	
Q4⩾0.82	4479	(33)	0.60 (0.39–0.91)		0.68 (0.43–1.06)		Q4⩾0.82	11138	(271)	1.03 (0.83–1.28)		0.95 (0.75–1.21)	

[a]Multivariate RRs calculated using the adjustment factors described in Material and methods. [b]Trend RRs calculated by 5 cm increase in height and in breast, waist and hip circumferences, 5 kg increase in weight, 2 kg/m² increase in BMI and 1–point increase in WHR. [c]Trend tests identical, whether BMI categorized into quartiles or WHO categories.

Among *postmenopausal* women, no variation in breast cancer risk with increasing height was observed. We observed nonsignificant positive trends in breast cancer risk with increasing weight and BMI. RRs for the fourth quartiles of weight and BMI compared with the first quartiles were 1.23 (0.97–1.57) and 1.21 (0.96–1.52), respectively. We observed a significant RR of 1.44 (1.04–1.99) when comparing women with a BMI greater than $30 \, kg/m^2$ with women with a BMI between 18.5 and $25 \, kg/m^2$.

RRs of breast cancer associated with thorax, breast, waist and hip circumferences and WHR are presented with and without additional adjustment for BMI. Among premenopausal women, significant negative trends in breast cancer risk associated with thorax, breast and waist circumferences were observed (*P* for trend $\leqslant 0.05$ for each). RRs for the fourth quartiles compared with the first quartiles of these variables were 0.70 (0.47–1.03), 0.68 (0.45–1.03) and 0.58 (0.38–0.88), respectively. No variation in risk associated with hip circumference was observed. We observed a nonsignificant negative trend in breast cancer risk with increasing WHR, with a RR of 0.60 (0.39–0.91) in the fourth quartile of WHR. Additional adjustment for BMI altered these results: the negative trend in risk with increasing thorax, breast and waist circumferences became nonsignificant and the associated RRs moved towards unity; the trend associated with hip circumference was reversed; an RR of 1.35 (0.79–2.32) in the fourth quartile of hip circumference was observed; and the RRs associated with WHR moved towards unity. However, the decrease in risk with increasing WHR was still apparent.

Among postmenopausal women, we observed significant positive trends in breast cancer risk with increasing thorax and waist circumferences (both p for trend $\leqslant 0.05$), with significant RRs of 1.24 (1.00–1.55) and 1.32 (1.04–1.66), respectively, in the third quartiles. Nonsignificant positive trends in breast cancer risk with increasing breast and hip circumference were observed. We observed no variation in breast cancer risk with increasing WHR. Additional adjustment for BMI moved all RRs towards unity and none of the relations remained significant.

HRT users were defined as women using HRT at the start of follow-up in 1995. The increase in breast cancer risk with increasing weight was greater among HRT nonusers, although nonsignificantly. The relationship with BMI was similar between HRT users and nonusers (Table 5). No difference on the other anthropometric characteristics was observed between HRT users and HRT nonusers (results not shown).

We estimated the risk of breast cancer according to the route of administration of HRT (Table 5). We defined as transdermal HRT users, women with more than 80% of their HRT administered transdermally. Others were considered as nontransdermal HRT users. We only present RRs of breast cancer according to weight and BMI cut into quartiles since the low prevalence of BMI under 18.5 or over $30 \, kg/m^2$ did not allow us to estimate RR in these categories.

No RR reached significance but the increase in risk of breast cancer with increasing weight and BMI seemed to be restricted to transdermal HRT users.

Table 5 Relative risks of postmenopausal breast cancer for all anthropometric measurements obtained from the fourth questionnaire (1995), by HRT use. E3N cohort

Variable	Total	Case	Multivariate[a] RRs	Total	Cases	Multivariate[a] RRs	Total	Cases	Multivariate[a] RRs	Total	Cases	Multivariate[a] RRs
		HRT nonusers			HRT users			Transdermal HRT users[b]			Nontransdermal HRT users[c]	
Weight (kg)												
Q1 <54	4043	(53)	1.00 (reference)	6274	(120)	1.00 (reference)	1912	(33)	1.00 (reference)	3862	(74)	1.00 (reference)
Q2 [54–60[	4631	(83)	1.10 (0.83–1.46)	7187	(148)	1.03 (0.83–1.29)	2135	(41)	1.08 (0.69–1.68)	4449	(92)	1.04 (0.77–1.41)
Q3 [60–66[	3496	(51)	0.91 (0.65–1.28)	5020	(98)	0.98 (0.76–1.26)	1516	(36)	1.30 (0.81–2.09)	3076	(60)	0.98 (0.69–1.39)
Q4 ⩾66	4741	(84)	1.22 (0.92–1.63)	4824	(106)	1.09 (0.84–1.42)	1515	(37)	1.43 (0.88–2.32)	2868	(59)	1.07 (0.74–1.53)
P for trend[a]		NS			NS			NS			NS	
BMI (kg/m²)												
Q1 <20.0	3856	(58)	1.00 (reference)	6272	(123)	1.00 (reference)	1877	(34)	1.00 (reference)	3931	(78)	1.00 (reference)
Q2 [20.0–22.8[	3672	(68)	1.02 (0.77–1.35)	6232	(124)	1.01 (0.81–1.27)	1835	(34)	0.98 (0.61–1.54)	3885	(76)	0.95 (0.69–1.29)
Q3 [22.8–25.1[	4259	(62)	0.94 (0.69–1.29)	5892	(119)	0.95 (0.75–1.23)	1771	(46)	1.38 (0.90–2.12)	3589	(69)	0.92 (0.67–1.27)
Q4 ⩾25.1	5124	(83)	1.07 (0.80–1.43)	4909	(106)	1.16 (0.90–1.49)	1595	(33)	1.16 (0.71–1.78)	2850	(62)	1.04 (0.75–1.47)
P for trend		NS			NS			NS			NS	
BMI (kg/m²)												
<18.5	509	(7)	0.61 (0.25–1.48)	676	(7)	0.63 (0.31–1.27)						
[18.5–25[	11031	(178)	1.00 (reference)	17397	(349)	1.00 (reference)						
[25–30[	4117	(59)	0.97 (0.72–1.31)	4454	(99)	1.11 (0.88–1.40)						
⩾30	1254	(27)	1.40 (0.91–2.17)	778	(17)	1.45 (0.90–2.33)						
P for trend		NS			NS							

[a]Multivariate RRs calculated using the adjustment factors described in Material and methods. [b]HRT users that more than 80% of their HRTs were administered in transdermal route, were considered as transdermal HRT users. Others were considered as nontransdermal HRT users. [c]Trend RRs calculated by 5 kg increase in weight, 2 kg/m² increase in BMI.

Discussion

Our study confirmed that the menopause is a turning point in the relation between anthropometric measurements and breast cancer risk. Weight, BMI, thorax and waist circumferences, and WHR were negatively related to breast cancer risk among premenopausal women, whereas thorax and waist circumferences were positively related to breast cancer risk among postmenopausal women. However, most of these relationships were explained by BMI, as additional adjustment for BMI moved RRs towards unity, particularly among postmenopausal women. No effect modification by HRT use was observed.

Among premenopausal women, previous studies, reviewed by Friedenreich,[3] reported heterogeneous results concerning *height*, with RRs of between 0.80 and 2.00 for taller women compared with shorter women. The increase in breast cancer risk with increasing height is in agreement with the RRs reported in a meta-analysis of seven cohort studies, the Pooling Project on Diet and Cancer.[2] Three recent case–control studies on Asian populations [10–12] showed an increased risk of premenopausal breast cancer among taller women (over approximately 160 cm). Among postmenopausal women, previous studies reported evidence of a positive association between height and breast cancer risk,[2,3,10,12] with RRs of between 1.3 and 1.9 for taller women compared with shorter women. Our results showed a weaker association, similar to that found in the study of Tung et al.[11]

When considering the relations between breast cancer risk and weight or BMI, we found contrasting results according to menopausal status. Among premenopausal women, our estimate of a negative relation between weight, BMI and breast cancer was similar to that of the Pooling Project on Diet and Cancer.[2] Other results from recent case–control studies on populations of various ethnic origins[3,12,13] were closer to unity. However, in case–control studies, because controls usually have many nonparticipants, those who are most obese are likely to be less represented. Among postmenopausal women, our results are similar to those of recent studies.[2,3,12,13,14]

Our results of a decrease in risk of premenopausal breast cancer with increasing thorax and waist circumferences are in agreement with previous studies.[2,12,15] The decrease in risk observed with increasing WHR is in disagreement with past studies and reviews,[3,6,12,15–17] which found a possible increase in risk of premenopausal breast cancer with increasing WHR. The highest increase in risk was observed in Männistö's analysis of a case–control study, with an RR of 4.6 (2.0–10.7) for women with a WHR greater than 0.87 compared with those with a WHR less than 0.78. A high WHR, indicating an android body shape, is commonly related to abdominal obesity [4,5,18] and to certain hormonal specificities which increase breast cancer risk: 1) an hyperinsulinaemia, an increase in Insulin-like growth factor I (IGF-I) activity resulting in a decrease in Sex Hormone Binding Globulin (SHBG) level,[19] and 2) higher levels of free oestrogen and testosterone due to a lower SHBG concentration.[20,21] An observational study by de Ridder [22] showed that women with abdominal obesity were generally obese (BMI > 30 kg/m^2), possibly indicating that an android body shape might be associated with a higher risk of premenopausal breast cancer only among obese women. However, Muti et al.[17] found a higher WHR associated with a higher risk of premenopausal breast cancer only among lean women.

Among postmenopausal women, thorax, breast, waist and hip circumferences were weakly positively related to breast cancer risk, in agreement with other studies.[3,12,14,15,23] WHR was not related to risk of postmenopausal breast cancer in our study, whereas other studies reported a positive relation, with recent studies [12,14,15,23] reporting a stronger relation than earlier ones, reviewed by Friedenreich.[3] Huang et al.[24] studied the independent effect of anthropometric measurements, with and without adjustment for BMI. The effects were increased when BMI was negatively correlated to the variable and attenuated when the correlation was positive. In our study, BMI was correlated positively with all anthropometric factors. All effects were attenuated when adjusting for BMI, but the effect of BMI on breast cancer risk remained significant in most analyses (results not shown). Thus in our cohort, risk of postmenopausal breast cancer was more dependent on overweight than on specific fat storage.

Previous studies found that overweight increased the risk of postmenopausal breast cancer to a greater degree in HRT never-users.[2,3,12,14,25] Our results showed a similar effect of overweight on breast cancer risk whatever HRT use. Among postmenopausal women, overweight, associated to lower levels of SHBG, results in a higher concentration of free oestrogen. Through their hepatocellular actions, oral oestrogens cause a sharp increase in SHBG level and a decrease in circulating IGF-I activity, whereas nonoral oestradiol administration has limited hepatocellular action.[26,27] These mechanisms might explain why postmenopausal breast cancer risk is not altered by overweight among HRT users in most studies primarily involving orally administered HRTs. Our results, and the fact that in our cohort, 70% of the HRT is used transdermally, give support to an effect modification by HRT use limited to HRT administered by an oral route.

Many studies have investigated the potential role of obesity in breast carcinogenesis.[3] In premenopause, the mechanism by which breast cancer risk would be decreased with obesity remains unclear. Recent studies indicated that in premenopause, the excess oestrogen synthesis in the adipose tissue would be downregulated by luteinizing hormone (LH) and follicular stimulating hormone (FSH).[20,28] However, Potischman et al.[29] observed that serum total oestradiol levels decrease with premenopausal obesity. The latter observation may be due to the fact that in premenopausal women, who are naturally oestrogenized, anovulation due to obesity results in a decrease in oestrogen and progesterone production.[30–32] Moreover, in a study on

premenopausal obese women, Potischman et al.[29] noted that injected radiolabelled oestrogen was sequestered by adipose tissue, reducing levels of free oestradiol. A global decrease in ovarian activity and oestrogen storage due to obesity would lead to a decreased risk of premenopausal breast cancer.

Several studies have shown a clear increase in total and free sex steroid levels with increased adiposity, after menopause.[21,29,33] After cessation of ovarian activity, sex steroids, particularly oestrogen, remain synthesized mainly in adipose tissue. Obesity is then positively correlated to plasma concentrations of testosterone and oestradiol. As obesity leads to insulinresistance and hyperinsulinæmia resulting in a decreased concentration of SHBG, combination of increased sex steroid synthesis and decreased SHBG concentration results in a global increase in plasma levels of free androgen and oestrogen.[20,21] Moreover, hyperinsulinaemia and insulin resistance, usual consequences of obesity, induce an increase in bioavailable IGF-I, growth factor involved in mammary tissue development and tumour promotion.[5,18] However, the hypothesis of a mechanism involving IGF-1 remains controversial.[34]

Our study has several limitations that need to be discussed. Although it is large, the E3N population is homogeneous and mainly consists of teachers, considered to be health conscious and leaner on average than French women in general. Our analyses are based on self-reported anthropometric measurements. Recent studies have shown good correlations between self-reported measurements of corpulence (such as BMI) and measurements by technicians.[35,36] We conducted our own validation study in the E3N cohort [37] that showed no significant differences between the anthropometric characteristics self-reported on a questionnaire and the same characteristics measured by technicians during a short interview. We also found,[37] like many other studies,[38–46] that obese subjects tend to underestimate their real anthropometric characteristics. However, because of the prospective design of our study, such misreporting would only bias our results towards unity.

In large cohort studies, measurements are taken at baseline and usually not updated. However, anthropometric characteristics can change between baseline and the moment an event occurs, especially in cohorts with a long follow-up.[3] We chose to focus on data measured in 1995, with a maximum follow-up time of 5 years between measurement and diagnosis or end of follow-up, so as to concentrate on risk associated with body shape rather than with changes in body shape.

In conclusion, our study shows that, in this particular cohort, overall obesity decreased the risk of premenopausal breast cancer and increased that of postmenopausal breast cancer, although to a lesser degree. An android body shape might possibly increase the risk of premenopausal breast cancer among obese women whereas it may decrease it in nonobese women. HRT use in the cohort did not alter the relations between anthropometric factors and the risk of postmenopausal breast cancer.

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