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Prediagnostic body size and breast cancer survival in the E3N cohort study

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Obesity has been associated with poor breast cancer prognosis, however most studies have focused on body mass index (BMI) and few have considered the distribution of adipose tissue. We investigated associations between prediagnostic adiposity and breast cancer survival, considering BMI, waist and hip circumferences (WC and HC), and waist-to-hip ratio (WHR).

Analyses included 3,006 women from the French E3N prospective cohort study diagnosed with primary invasive breast cancer between 1995 and 2008. We investigated overall, breast cancer-specific, and disease-free survival, overall and according to stage, menopausal and hormonal status and year of diagnosis, using Cox proportional hazard models adjusted for tumor characteristics and lifestyle risk factors.

Women with a prediagnostic HC > 100 cm were at increased risk of death from all causes (hazard ratio (HR)$_{>100 vs < 95\ cm}$ = 1.38, 95% Confidence Interval (CI) = 1.02–1.86, P_{trend} = 0.02) and from breast cancer (HR$_{>100 vs < 95\ cm}$ = 1.50, CI = 1.03–2.17, P_{trend} = 0.03), and of second invasive cancer event (HR$_{>100 vs < 95\ cm}$ = 1.36, CI = 1.11–1.67, P_{trend} = 0.002), compared to those with HC <95 cm. Associations were stronger after adjustment for BMI. BMI, WC and WHR were not associated with survival after breast cancer.

Our study underlines the importance of going beyond BMI when studying the association between adiposity and breast cancer survival. Further studies should be conducted to confirm our results on hip circumference.

Key words: breast cancer survival, adiposity, obesity, mortality, disease-free survival

Abbreviations: BCSS: breast cancer-specific survival; BMI: body mass index; CI: confidence interval; ER: estrogen receptor; HC: hip circumference; HR: hazard ratio; iDFS: invasive disease-free survival; MHT: menopausal hormone therapy; OS: overall survival; PR: progesterone receptor; WC: waist circumference; WHR: waist-to-hip ratio

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Breast cancer is the most prevalent cancer in women in both developed and developing countries.[1] With 5-year relative survival rates of 80% or more in developed countries,[2] an increasing number of women are currently living with a diagnosis of breast cancer. For these cancer survivors, it is essential to identify modifiable risk factors that could influence their prognosis.

Breast cancer characteristics such as TNM stage, lymph node status, tumor size, tumor grade, histological type, lymphatic and vascular invasion, hormone receptor and HER2 status, and age at diagnosis are known predictive or prognostic factors.[3,4] A recent meta-analysis conducted by the World Cancer Research Fund (WCRF) has shown that obesity and excess weight before diagnosis were associated with increased mortality (from all causes and from breast cancer).[5] However, the WCRF expert panel judged that the level of evidence for the association between a healthy body mass index (BMI) and a better survival was only limited, despite suggestive evidence.[6] Weaknesses have been underlined in observational studies as well as in clinical trials. In particular, cohort studies need to assess more systematically important prognostic factors, such as tumor characteristics, treatment or time period of cancer diagnosis (because of rapid changes in treatments). On the other hand, results from clinical trials, which

What's new?

If you're fat, you're less likely to survive breast cancer—but does it matter where that fat is on your body? Perhaps, according to a new report. These authors noted that previous work only considers the patient's BMI when studying prognosis. This study tested hip and waist circumference as well. They discovered that women with larger hip circumference had greater risk of death from all causes and from breast cancer, and of second invasive cancer than had women with smaller hips. No association was found with waist circumference or BMI, suggesting there's more to the story than BMI when it comes to cancer survival.

often include such information, do not sufficiently take into account lifestyle factors and are more difficult to generalize because of selection bias in the survivors participating in clinical trials compared with the overall population of survivors. In addition, most published studies have considered only BMI, an overall measurement of adiposity. They rarely considered waist and hip circumferences (WC and HC) or waist-to-hip ratio (WHR),[7] measures of abdominal or gluteofemoral adiposity, which may have a different impact on health than overall adiposity (BMI),[8,9] in particular with respect to cancer risk.[10]

In this context, our objective was to study the associations between several measurements of prediagnostic adiposity (BMI, WC, HC, WHR) and breast cancer survival, overall and in breast cancer subtypes, accounting for major potential confounders, using data from the large E3N prospective cohort study.

Methods

The E3N cohort study

The "Etude Epidémiologique auprès des Femmes de la Mutuelle Générale de l'Education Nationale" (E3N) study is a prospective cohort study initiated in 1990.[11] Overall, 98,995 women aged 40–65 years were recruited from a national health insurance plan covering mostly teachers. All women gave informed consent, in compliance with the rules of the French National Commission for Data Protection and Privacy, the organization that gave ethical approval for the study. Follow-up questionnaires have been sent every 2–3 years to the participants since 1990, collecting data about lifestyle and reproductive factors as well as major health events, including cancer.

Outcome assessment

Any new diagnosis of cancer event (primary tumors and loco-regional or distant recurrences) reported every two to three years in each follow-up questionnaire up to December 7, 2011 was systematically investigated and validated using pathological reports collected from the patients or their doctors. Tumor characteristics such as stage, grade, nodes, distant metastases, size of the tumor, hormonal receptor status and histological subtype were extracted from pathological reports or any other medical document (such as bone-scan, magnetic resonance imaging (MRI) or X-ray radiography reports).

We considered three outcomes after primary invasive breast cancer: second invasive cancer events, deaths from breast cancer and deaths from any cause. We considered as second invasive cancer events loco-regional invasive recurrences, distant recurrences (metastases) or a second invasive cancer of any primary sites up to December 2011. All cancer events diagnosed within a same three-month period were considered as synchronous events.[12–15]

The participants' vital status was regularly updated through the health insurance plan, postal service and next-of-kin; causes of death were obtained from the French National Service on Causes of Death. When breast cancer was reported as the initial cause of death at least 2 years after the initial breast cancer diagnosis without any cancer event reported since the breast cancer diagnosis ($N = 17$), we considered that the participant had suffered distant recurrence 2 years before death. These 2 years correspond to the median survival time for women of the study population diagnosed with metastases, and have also been used in similar cohort studies.[16] When time between breast cancer diagnosis and death from breast cancer was <2 years ($N = 21$), the date of distant recurrence was defined as the date of death.[16]

Anthropometric measurements

Each follow-up questionnaire asked women to provide their weight in kilograms. Height (cm) was collected in 1990, 1995 and in all questionnaires since 2000. BMI was then computed according to the weight reported in each questionnaire as weight (kg)/[height (m) $\times$ height (m)].

Women were asked to report their waist and hip circumferences according to precise instructions in the 1995, 2002 and 2005 questionnaires.[17] Waist circumference was defined as the smallest circumference between the base of the ribs and the largest point of the iliac crest, and hip circumference as the largest circumference below the umbilicus. Waist-to-hip ratio was then computed as waist circumference/hip circumference.

Study population

Only women with no personal history of cancer, except basal cell skin carcinoma, prior to breast cancer diagnosis, and whose first primary invasive breast cancer had been

confirmed by a pathological report before June 25, 2008 ($N = 5991$, 93.5%), were included in the study. We excluded women with incomplete date of any cancer event or death ($N = 133$), *in situ* breast cancer ($n = 760$), phyllode tumors or tumors with missing morphological codes ($n = 7$), or metastatic disease at diagnosis ($n = 39$). In addition, participants who had no data on BMI, WC or HC before their first primary breast cancer diagnosis were excluded ($N = 1{,}892$). The study population included 3160 cancer cases diagnosed between 1995 (first available data on WC and HC) and June 25, 2008 (date when the validation of first cancer cases was considered complete).

Statistical analyses

Survival follow-up started at the date of diagnosis of the first primary invasive breast cancer. We defined invasive disease-free survival (iDFS) as time to second invasive cancer event or death from any cause, overall survival (OS) as time to death from any cause and breast cancer-specific survival (BCSS) as time to death from breast cancer, as recommended by Hudis *et al.*[12] and Gourgou-Bourgade *et al.*[18] For OS and BCSS analyses, women were followed until the event of interest or until December 7, 2011. Women who did not answer the last questionnaire (11.0%) were considered lost to follow-up in the iDFS analyses, and censored at the date of the last completed questionnaire plus 6 months. Otherwise, women were followed until the date of diagnosis of a second invasive cancer event, or the first date between date of death, or December 7, 2011 in iDFS analyses.

For descriptive analyses, differences across World Health Organization (WHO) BMI categories [<25 kg/m^2, 25–30 kg/m^2 (overweight), ≥ 30 kg/m^2 (obese)[19]; Table 1] were assessed using χ^2 tests or analyses of variance depending on the type of variables.

Cox proportional hazards models with time since diagnosis (in months) as the timescale were used to estimate hazard ratios (HRs) and 95% confidence intervals (CI) associated with categories of anthropometric measurements (WHO categories for BMI, and tertiles for HC, WC and WHR), using the last anthropometric measurements available before diagnosis of the first primary invasive breast cancer. Proportional hazards assumption was assessed using log–log plots. For tests of linear trend across categories, we assigned participants the median value for each anthropometric measurement category and modeled the corresponding variable as a continuous term.

Model 1 was adjusted for age at diagnosis, time between exposure assessment and diagnosis, tumor characteristics (Scarff–Bloom–Richardson (SBR) grade of the tumor, estrogen receptor (ER) status, progesterone receptor (PR) status, TNM stage, histological subtype), as well as for hormonal and lifestyle factors at diagnosis: menopausal status, age at menopause, use of menopausal hormone therapy (MHT), use of oral contraceptives, parity, history of benign breast disease, family history of breast cancer in first-degree relatives, smoking status, education level, diabetes and total physical activity in 1990 (MET h/week). HER2 status was available only for 266 women, thus it was not included in the analyses. Mutual adjustments for WC and BMI were added in model 2. All models were stratified according to period of diagnosis (1995–1999; 2000–2004; 2005–2008).

Adjustments for dietary factors such as daily energy and alcohol intakes in 1993 were examined on the sub-population ($N = 2822$) for which dietary intake data were available, after exclusion of subjects with extreme energy intakes. Since estimates remained similar, dietary variables were not included in the final models. For covariates with $<5\%$ missing values, missing values were imputed to the modal category or the median value. For SBR grade and hormone receptor status, we created a missing category.

Analyses were further stratified according to TNM stage (stage I or stage II–III), menopausal status at diagnosis (premenopause or postmenopause), ER/PR status and period of diagnosis (before or after 2000).

Sensitivity analyses were performed excluding women with a BMI <18.5 kg/m^2 ($n = 76$, 2.4%), women whose last available BMI measurement was reported over 2 years before diagnosis ($n = 1017$) and excluding women whose second event was not confirmed by medical document ($n = 135$).

All statistical tests were two-sided, and p values below 0.05 were considered statistically significant. All analyses were performed with the Statistical Analyses Systems (SAS) version 9.3 (SAS Institute, Cary, NC).

Results

In our study population, 286 women had died before December 2011, of whom 188 because of their breast cancer (among which 130 were stage II or III), and 614 experienced a second invasive cancer event, either loco-regional invasive recurrence ($N = 183$), distant metastasis ($N = 211$), second primary invasive tumor ($N = 112$), uncertain whether primary tumor or metastatic disease ($N = 3$) or unclassified cancer event without any pathological report ($N = 105$). Overall, 78% of second events were confirmed by a medical document (pathological or medical imaging reports, death certificate).

Mean follow-up was 9.1 years for OS and BCSS, and 8.0 years for iDFS (Table 1). Mean age at diagnosis was 61.5 years and most cases (90.8%) were diagnosed after menopause. Breast cancer cases were mostly ductal (72.5%), TNM stage I (63.5%), well or moderately differentiated (82.5% SBR grade 1 and 2), and, for tumors with known hormone receptor status, ER positive (82.7%) and PR positive (64.5%). Mean BMI before diagnosis was 23.8 kg/m^2 (WC: 78.6 cm, HC: 98.3 cm, WHR: 0.80) and was assessed on average 19.2 months before diagnosis. Obese and overweight women had a higher prevalence of hormone receptor positive tumors and were older at diagnosis. Obese and overweight women were less likely to have used oral contraceptives or menopausal hormone therapy, and were more often diabetics.

Table 1. Baseline characteristics of the study population according to body mass index (BMI) categories

Variable	All breast cancer cases *N* = 3160 Mean (Std) or *N* (%)	<25 kg/m^2 *N* = 2196 Mean (Std) or *N* (%)	25–30 kg/m^2 *N* = 770 Mean (Std) or *N* (%)	≥30 kg/m^2 *N* = 194 Mean (Std) or *N* (%)	Missing values	*p*-value[1]
Follow-up for OS and BCSS (years)	9.13 (3.65)	9.42 (3.69)	8.57 (3.49)	8.07 (3.42)		*<0.0001*
Follow-up for iDFS (years)	7.98 (3.91)	8.24 (3.97)	7.44 (3.72)	7.14 (3.49)		*<0.0001*
Year of diagnosis						*<0.0001*
1995–1999	935 (29.5%)	712 (32.4%)	185 (24.0%)	38 (19.6%)		
2000–2004	1348 (42.7%)	939 (42.8%)	324 (42.1%)	85 (43.8%)		
2005–2008	877 (27.8%)	545 (24.8%)	261 (33.9%)	71 (36.6%)		
Age at cancer diagnosis (years)	61.45 (7.02)	60.72 (7.07)	62.97 (6.58)	63.72 (6.71)		*<0.0001*
TNM stage at diagnosis					89 (3.0%)	*0.1*
Stage I	1949 (63.5%)	1385 (64.9%)	452 (60.8%)	112 (58.7%)		
Stage II	924 (30.1%)	616 (28.8%)	239 (32.1%)	69 (36.1%)		
Stage III	198 (6.4%)	135 (6.3%)	53 (7.1%)	10 (5.2%)		
Scarff–Bloom–Richardson grade					306 (10.0%)	*0.6*
1	985 (34.5%)	693 (35.1%)	235 (33.8%)	57 (31.5%)		
2	1369 (48.0%)	930 (47.0%)	346 (49.7%)	93 (51.4%)		
3	500 (17.5%)	354 (17.9%)	115 (16.5%)	31 (17.1%)		
ER and PR status					369 (11.7%)	*0.02*
ER+PR+	1713 (61.4%)	1144 (59.3%)	447 (65.3%)	122 (68.9%)		
ER+PR−	579 (20.8%)	415 (21.5%)	132 (19.3%)	32 (18.1%)		
ER−PR+	87 (3.1%)	67 (3.5%)	14 (2.0%)	6 (3.4%)		
ER−PR−	412 (14.8%)	303 (15.7%)	92 (13.4%)	17 (9.6%)		
Histological subtypes					0	*0.9*
Ductal	2290 (72.5%)	1590 (72.4%)	559 (72.6%)	141 (72.7%)		
Lobular	536 (17.0%)	375 (17.1%)	131 (17.0%)	30 (15.5%)		
Mixed	76 (2.4%)	50 (2.3%)	21 (2.7%)	5 (2.6%)		
Other	258 (8.1%)	181 (8.2%)	59 (7.7%)	18 (9.2%)		
Use of oral contraceptive					0	*<0.0001*
Ever	1891 (59.8%)	1369 (62.3%)	436 (56.6%)	86 (44.3%)		
Never	1269 (40.2%)	827 (37.7%)	334 (43.4%)	108 (55.7%)		
Number of children					22 (1.0%)	*0.002*
0	412 (13.1%)	293 (13.5%)	97 (12.6%)	22 (11.4%)		
1	525 (16.7%)	387 (17.7%)	108 (14.2%)	30 (15.5%)		
2	1393 (44.4%)	995 (45.6%)	319 (41.9%)	79 (40.9%)		
3	627 (20.0%)	398 (18.2%)	181 (23.8%)	48 (24.9%)		
>3	181 (5.8%)	110 (5.0%)	57 (7.5%)	14 (7.3%)		
Menopausal status					19 (1.0%)	*<0.0001*
Postmenopause	2853 (90.8%)	1936 (88.7%)	730 (95.2%)	187 (97.4%)		
Premenopause	288 (9.2%)	246 (11.3%)	37 (4.8%)	5 (2.6%)		
Age of menopause (years)	50.79 (3.51)	50.87 (3.36)	50.60 (3.77)	50.64 (4.08)	15 (0.5%)	*0.1*
Use of hormonal treatment of menopause					0	*<0.0001*
Current	1542 (48.8%)	1116 (53.4%)	314 (43.6%)	49 (27.4%)		
Past	544 (17.2%)	285 (13.6%)	163 (22.7%)	41 (22.9%)		

Table 1. Baseline characteristics of the study population according to body mass index (BMI) categories (Continued)

Variable	All breast cancer cases *N* = 3160 Mean (Std) or *N* (%)	<25 kg/m² *N* = 2196 Mean (Std) or *N* (%)	25–30 kg/m² *N* = 770 Mean (Std) or *N* (%)	≥30 kg/m² *N* = 194 Mean (Std) or *N* (%)	Missing values	*p*-value[1]
Never	786 (24.9%)	447 (21.3%)	206 (28.7%)	84 (46.9%)		
Premenopausal	288 (9.1%)	246 (11.7%)	36 (5.0%)	5 (2.8%)		
History of benign breast disease					0	*<0.0001*
Yes	1391 (44.0%)	1026 (46.7%)	303 (39.4%)	62 (32.0%)		
No	1769 (56.0%)	1170 (53.3%)	467 (60.6%)	132 (68.0%)		
Family history of breast cancer					35 (1.0%)	*0.6*
Yes	562 (18.0%)	382 (17.6%)	142 (18.6%)	38 (19.8%)		
No	2563 (82.0%)	1788 (82.4%)	621 (81.4%)	154 (80.2%)		
Education level					121 (4.0%)	*<0.0001*
Undergraduate	322 (10.6%)	184 (8.7%)	105 (14.3%)	33 (17.7%)		
0–2 years postgraduation	1535 (50.5%)	1058 (49.9%)	372 (50.8%)	105 (56.8%)		
3–4 years postgraduation	562 (18.5%)	418 (19.7%)	118 (16.1%)	26 (14.1%)		
≥ 5 years postgraduation	620 (20.4%)	461 (21.7%)	138 (18.8%)	21 (11.4%)		
Smoking status					12 (0.0%)	*0.01*
Current	304 (9.6%)	234 (10.7%)	50 (6.5%)	20 (10.5%)		
Past	1186 (37.7%)	826 (37.7%)	286 (37.4%)	74 (38.5%)		
Never	1658 (52.7%)	1131 (51.6%)	429 (56.1%)	98 (51.0%)		
Total physical activity (MET h/week)	41.16 (25.93)	41.03 (25.42)	41.75 (26.64)	40.23 (28.79)	46 (1.5%)	*0.3*
Energy intake without alcohol (kcal/day)	2149.2 (517.08)	2145.2 (508.26)	2136.3 (523.81)	2252.2 (584.46)	338 (10.7%)	*0.07*
Alcohol intake (g/day)	12.82 (15.02)	12.40 (14.20)	13.09 (15.20)	16.89 (22.02)	338 (10.7%)	*0.2*
Diabetes					0	*<0.0001*
Yes	98 (3.1%)	37 (1.7%)	36 (4.7%)	25 (12.9%)		
No	3062 (96.9%)	2159 (98.3%)	734 (95.3%)	169 (87.1%)		
BMI (kg/m²)	23.77 (3.64)	21.88 (1.81)	26.82 (1.33)	33.04 (2.91)		*<0.0001*
Waist circumference (cm)	78.57 (9.95)	74.28 (6.31)	85.46 (7.65)	99.81 (8.97)		*<0.0001*
Hip circumference (cm)	98.31 (8.58)	94.65 (5.81)	104.22 (5.95)	116.37 (7.75)		*<0.0001*
Waist-to-hip ratio	0.80 (0.06)	0.79 (0.06)	0.82 (0.06)	0.86 (0.07)		*<0.0001*
Time between BMI measure and diagnosis (months)	19.17 (13.22)	18.70 (12.67)	20.04 (13.58)	21.05 (17.11)		*0.09*

[1] *p*-values for comparison across BMI categories by analysis of variance on log-transformed continuous variables and χ^2 test for categorical variables.

Abbreviations: OS: overall survival; BCSS: breast cancer-specific survival; iDFS: invasive disease-free survival; ER: estrogen receptor; PR: progesterone receptor.

In models adjusted for tumor characteristics and lifestyle factors (model 1), neither BMI nor WC or WHR were associated with any of the outcomes (Table 2). High HC was associated with an increased risk of death from all causes (OS: $HR_{>100 vs < 95\ cm} = 1.38$, CI = 1.02–1.86, $P_{trend} = 0.02$), breast cancer-specific death (BCSS: $HR_{>100 vs < 95\ cm} = 1.50$, CI = 1.03–2.17, $P_{trend} = 0.03$), and second invasive cancer events (iDFS: $HR_{>100 vs < 95\ cm} = 1.36$, CI = 1.11–1.67, $P_{trend} = 0.002$). Additional adjustment for BMI strengthened the associations (OS: $HR_{>100 vs < 95\ cm} = 1.76$, CI = 1.20–2.59, $P_{trend} = 0.003$; BCSS: $HR_{\geq 100 vs < 95\ cm} = 1.66$, CI = 1.03–2.67, $P_{trend} = 0.03$; iDFS: $HR_{>100 vs < 95\ cm} = 1.58$, CI = 1.22–2.06, $P_{trend} = 0.0005$).

Associations with HC did not differ in analyses stratified according to TNM stage (Table 3). Stage I cases with high WC were at increased risk of a second invasive cancer event (but not death) (Model 1: $HR_{>80 vs < 74\ cm} = 1.42$, CI = 1.06–1.92, $P_{trend} = 0.02$, Model 2: $HR_{>80\ vs < 74\ cm} = 1.61$, CI = 1.08–2.39, $P_{trend} = 0.02 - P_{interaction} = 0.28$) while no association was observed with WC in women with cancer of stage II or III.

Table 2. Associations between anthropometric variables before diagnosis and overall survival (OS), breast cancer specific survival (BCSS) and invasive disease-free survival (iDFS) after breast cancer in the E3N cohort study

	OS					BCSS					iDFS				
		Model 1[1]		Model 2[2]			Model 1[1]		Model 2[2]			Model 1[1]		Model 2[2]	
	Events[3]	HR	95% CI	HR	95% CI	Events[4]	HR	95% CI	HR	95% CI	Events[5]	HR	95% CI	HR	95% CI
BMI (kg/m^2)															
5 kg/m^2	286	1.01	(0.85–1.20)	1.03	(0.79–1.34)	188	1.09	(0.90–1.34)	1.16	(0.85–1.59)	620	1.04	(0.93–1.17)	1.01	(0.84–1.22)
<25	193	1.00	(ref)	1.00	(ref)	123	1.00	(ref)	1.00	(ref)	422	1.00	(ref)	1.00	(ref)
25–30	74	1.06	(0.80–1.4)	1.09	(0.78–1.52)	51	1.2	(0.85–1.70)	1.32	(0.87–1.99)	165	1.17	(0.97–1.41)	1.14	(0.91–1.43)
≥30	19	1.00	(0.60–1.66)	1.05	(0.55–2.02)	14	1.4	(0.77–2.53)	1.72	(0.79–3.75)	33	0.97	(0.67–1.40)	0.92	(0.57–1.46)
P-trend			*0.82*		*0.75*			*0.17*		*0.12*			*0.44*		*0.78*
Waist circumference (cm)															
<74	94	1.00	(ref)	1.00	(ref)	65	1.00	(ref)	1.00	(ref)	214	1.00	(ref)	1.00	(ref)
74–80	100	1.17	(0.88–1.57)	1.15	(0.85–1.55)	62	1.07	(0.75–1.53)	1.00	(0.69–1.46)	204	1.15	(0.94–1.39)	1.15	(0.93–1.41)
>80	92	0.96	(0.70–1.32)	0.89	(0.59–1.35)	61	0.99	(0.67–1.46)	0.82	(0.50–1.35)	202	1.14	(0.93–1.41)	1.14	(0.87–1.50)
P-trend			*0.69*		*0.54*			*0.93*		*0.42*			*0.23*		*0.35*
Hip circumference (cm)															
<95	87	1.00	(ref)	1.00	(ref)	56	1.00	(ref)	1.00	(ref)	195	1.00	(ref)	1.00	(ref)
95–100	81	0.99	(0.72–1.35)	1.08	(0.78–1.49)	56	1.14	(0.77–1.68)	1.18	(0.79–1.76)	197	1.09	(0.89–1.34)	1.15	(0.94–1.43)
>100	118	1.38	(1.02–1.86)	1.76	(1.20–2.59)	76	1.50	(1.03–2.17)	1.66	(1.03–2.67)	228	1.36	(1.11–1.67)	1.58	(1.22–2.06)
P-trend			*0.02*		*0.003*			*0.03*		*0.03*			*0.002*		*0.0005*
Waist-to-hip ratio															
<0.77	107	1.00	(ref)	1.00	(ref)	69	1.00	(ref)	1.00	(ref)	223	1.00	(ref)	1.00	(ref)
0.77–0.82	90	0.89	(0.67–1.19)	0.89	(0.66–1.18)	62	0.94	(0.66–1.34)	0.92	(0.65–1.32)	221	1.14	(0.94–1.38)	1.13	(0.93–1.36)
>0.82	89	0.83	(0.61–1.13)	0.81	(0.59–1.12)	57	0.82	(0.56–1.20)	0.78	(0.52–1.15)	176	0.94	(0.76–1.16)	0.91	(0.73–1.14)
P-trend			*0.23*		*0.20*			*0.31*		*0.21*			*0.57*		*0.43*

[1]Model 1 was adjusted for age at diagnosis, time between exposure measurement and diagnosis, Scarff–Bloom–Richardson (SBR) grade of the tumor (I/II/III), estrogen receptors status (positive/negative/missing), progesterone receptors status (positive/negative/missing),TNM stage (I/II/III), histological subtype (ductal/lobular/mixed/other), menopausal status at diagnosis, age of menopause, use of hormonal treatment of menopause (current/past/never/missing/premenopause), use of oral contraceptive (ever/never), number of biological children (0/1/2/3/>3), history of benign breast disease (yes/no), family history of breast cancer (yes/no), smoking status (current smoker/former smoker/never smoker), education level (undergraduate/0–2 years postgraduation/3–4 years postgraduation/≥5 years postgraduation), diabetes (yes/no) and total physical activity (MET h/week) at first questionnaire. Model 1 was also stratified on year of diagnosis (1995–1999/2000–2004/2005–2008). [2]Model 2 was adjusted on waist circumference when BMI was the exposure, and adjusted on BMI for other anthropometric measurements. [3]Deaths (all causes). [4]Deaths from breast cancer. [5]Second cancer event or death from any cause.
Abbreviations: HR: hazard ratio; CI: confidence interval; BMI: body mass index.

Table 3. Associations between anthropometric variables before diagnosis and overall mortality and iDFS after breast cancer according to TNM stage at diagnosis in the E3N cohort

	OS												iDFS									
	STAGE I (*N* = 2038)					STAGE II-III (*N* = 1122)					*P-interaction*		STAGE I (*N* = 2038)					STAGE II-III (*N* = 1122)					*P-interaction*	
		Model 1[1]		Model 2[2]			Model 1[1]		Model 2[2]		M1	M2		Model 1[1]		Model 2[2]			Model 1[1]		Model 2[2]		M1	M2
	Events[3]	HR	95% CI	HR	95% CI	Events[4]	HR	95% CI	HR	95% CI			Events[3]	HR	95% CI	HR	95% CI	Events[4]	HR	95% CI	HR	95% CI		
BMI (kg/m^2)																								
5 kg/m^2	111	0.98	(0.73–1.31)	0.75	(0.46–1.20)	175	0.95	(0.78–1.17)	1.08	(0.77–1.51)	*0.46*	*0.46*	315	1.07	(0.91–1.27)	0.88	(0.67–1.17)	305	1.01	(0.86–1.18)	1.16	(0.89–1.51)	*0.29*	*0.28*
<25	78	1.00	(ref)	1.00	(ref)	115	1.00	(ref)	1.00	(ref)	*0.85*	*0.85*	216	1.00	(ref)	1.00	(ref)	206	1.00	(ref)	1.00	(ref)	*0.05*	*0.05*
25–30	28	0.96	(0.61–1.51)	0.77	(0.44–1.34)	46	1.00	(0.69–1.43)	1.12	(0.72–1.73)			89	1.44	(1.11–1.86)	1.26	(0.91–1.74)	76	0.95	(0.72–1.26)	1.04	(0.75–1.45)		
≥30	5	0.89	(0.35–2.27)	0.54	(0.17–1.74)	14	0.86	(0.47–1.57)	1.11	(0.49–2.52)			10	0.74	(0.39–1.41)	0.54	(0.25–1.19)	23	1.06	(0.67–1.67)	1.32	(0.71–2.45)		
P-trend			*0.77*		*0.25*			*0.69*		*0.71*					*0.31*		*0.77*			*0.99*		*0.46*		
Waist circumference (cm)																								
<74	34	1.00	(ref)	1.00	(ref)	60	1.00	(ref)	1.00	(ref)	*0.35*	*0.35*	109	1.00	(ref)	1.00	(ref)	105	1.00	(ref)	1.00	(ref)	*0.28*	*0.28*
74–80	43	1.53	(0.96–2.44)	1.60	(0.98–2.63)	57	0.94	(0.64–1.36)	0.92	(0.62–1.35)			106	1.31	(0.99–1.72)	1.37	(1.02–1.83)	98	0.94	(0.71–1.24)	0.91	(0.67–1.22)		
>80	34	1.14	(0.68–1.92)	1.28	(0.65–2.51)	58	0.80	(0.54–1.18)	0.74	(0.44–1.25)			100	1.42	(1.06–1.92)	1.61	(1.08–2.39)	102	0.89	(0.66–1.20)	0.81	(0.54–1.20)		
P-trend			*0.73*		*0.57*			*0.25*		*0.26*					*0.02*		*0.02*			*0.47*		*0.29*		
Hip circumference (cm)																								
<95	34	1.00	(ref)	1.00	(ref)	53	1.00	(ref)	1.00	(ref)	*0.83*	*0.79*	109	1.00	(ref)	1.00	(ref)	86	1.00	(ref)	1.00	(ref)	*0.67*	*0.70*
95–100	36	1.20	(0.74–1.94)	1.41	(0.83–2.38)	45	0.85	(0.56–1.29)	1.03	(0.66–1.61)			101	1.07	(0.81–1.41)	1.11	(0.83–1.50)	96	1.05	(0.78–1.43)	1.16	(0.84–1.60)		
>100	41	1.40	(0.85–2.29)	2.05	(1.02–4.11)	77	1.39	(0.95–2.04)	2.33	(1.37–3.97)			105	1.34	(1.00–1.79)	1.49	(1.00–2.22)	123	1.34	(0.99–1.81)	1.73	(1.15–2.61)		
P-trend			*0.19*		*0.04*			*0.04*		*0.0008*					*0.04*		*0.046*			*0.04*		*0.007*		
Waist-to-hip ratio																								
<0.77	43	1.00	(ref)	1.00	(ref)	64	1.00	(ref)	1.00	(ref)	*0.56*	*0.54*	109	1.00	(ref)	1.00	(ref)	114	1.00	(ref)	1.00	(ref)	*0.12*	*0.10*
0.77–0.82	32	0.89	(0.56–1.42)	0.89	(0.56–1.43)	58	0.93	(0.64–1.35)	0.93	(0.64–1.35)			114	1.35	(1.03–1.76)	1.34	(1.02–1.75)	107	1.04	(0.79–1.38)	1.03	(0.78–1.37)		
>0.82	36	1.00	(0.62–1.62)	1.01	(0.61–1.66)	53	0.73	(0.49–1.08)	0.73	(0.48–1.10)			92	1.29	(0.96–1.73)	1.27	(0.93–1.72)	84	0.72	(0.53–0.98)	0.70	(0.51–0.95)		
P-trend			*0.99*		*0.98*			*0.11*		*0.13*					*0.08*		*0.11*			*0.03*		*0.02*		

[1]Model 1 was adjusted for age at diagnosis, time between exposure measurement and diagnosis, Scarff–Bloom–Richardson (SBR) grade of the tumor (I/II/III), estrogen receptors status (positive/negative/missing), progesterone receptors status (positive/negative/missing), histological subtype (ductal/lobular/mixed/other), menopausal status at diagnosis, age of menopause, use of hormonal treatment of menopause (current/past/never/missing/premenopause), use of oral contraceptive (ever/never), number of biological children (0/1/2/3/>3), history of benign breast disease (yes/no), family history of breast cancer (yes/no), smoking status (current smoker/former smoker/never smoker), education level (undergraduate/0–2 years postgraduation/3–4 years postgraduation/≥5 years postgraduation), diabetes (yes/no) and total physical activity (MET h/week) at first questionnaire. Model 1 was also stratified on year of diagnosis (1995–1999/2000–2004/2005–2008). [2]Model 2 was adjusted on waist circumference when BMI was the exposure, and adjusted on BMI for other anthropometric measurements. [3]Deaths (all causes). [4]Second cancer event or death from any cause.

Abbreviations: OS: overall survival; iDFS: invasive disease free survival; HR: hazard ratio; CI: confidence interval; BMI: body mass index.

Table 4. Associations between anthropometric variables before diagnosis and overall mortality and iDFS after breast cancer according to estrogen and progesterone receptor status of the tumors in the E3N cohort

	OS												iDFS									
	ER + PR+ (*N* = 1713)					ER − PR− (*N* = 1713)					*P-interaction*		ER + PR+ (*N* = 1713)					ER − PR− (*N* = 412)					*P-interaction*	
		Model 1[1]		Model 2[2]			Model 1[1]		Model 2[2]		M1	M2		Model 1*		Model 2§			Model 1*		Model 2§		M1	M2
	Events[3]	HR	95% CI	HR	95% CI	Events[4]	HR	95% CI	HR	95% CI			Events[3]	HR	95% CI	HR	95% CI	Events[4]	HR	95% CI	HR	95% CI		
BMI (kg/m^2)																								
5 kg/m^2	123	0.86	(0.66–1.11)	0.84	(0.55–1.27)	59	1.14	(0.77–1.70)	1.52	(0.79–2.92)	*0.16*	*0.16*	293	0.89	(0.75–1.06)	0.9	(0.68–1.20)	122	1.29	(1.01–1.64)	1.4	(0.90–2.18)	*0.37*	*0.38*
<25	83	1.00	(ref)	1.00	(ref)	43	1.00	(ref)	1.00	(ref)	*0.10*	*0.10*	203	1.00	(ref)	1.00	(ref)	87	1.00	(ref)	1.00	(ref)	*0.16*	*0.16*
25–30	30	0.80	(0.51–1.25)	0.81	(0.47–1.41)	15	1.27	(0.63–2.55)	1.42	(0.62–3.23)			75	0.96	(0.72–1.27)	0.98	(0.69–1.39)	30	1.29	(0.81–2.04)	1.14	(0.65–1.98)		
≥30	10	0.75	(0.36–1.55)	0.78	(0.29–2.10)	1	0.90	(0.11–7.18)	1.21	(0.11–13.17)			15	0.66	(0.38–1.15)	0.7	(0.35–1.42)	5	1.40	(0.53–3.71)	1.03	(0.30–3.52)		
P-trend			*0.29*		*0.52*			*0.66*		*0.50*					*0.20*		*0.45*			*0.23*		*0.78*		
Waist circumference (cm)																								
<74	40	1.00	(ref)	1.00	(ref)	24	1.00	(ref)	1.00	(ref)	*0.48*	*0.48*	100	1.00	(ref)	1.00	(ref)	46	1.00	(ref)	1.00	(ref)	*0.86*	*0.86*
74-80	45	1.19	(0.76–1.87)	1.21	(0.76–1.94)	18	0.91	(0.44–1.85)	0.78	(0.36–1.70)			99	1.09	(0.82–1.46)	1.16	(0.86–1.58)	37	1.02	(0.63–1.63)	0.87	(0.52–1.44)		
>80	38	0.73	(0.44–1.22)	0.77	(0.40–1.48)	17	0.94	(0.44–2.03)	0.69	(0.25–1.87)			94	0.95	(0.69–1.30)	1.14	(0.75–1.74)	39	1.25	(0.77–2.03)	0.83	(0.43–1.61)		
P-trend			*0.16*		*0.39*			*0.89*		*0.48*					*0.67*		*0.57*			*0.35*		*0.60*		
Hip circumference (cm)																								
<95	40	1.00	(ref)	1.00	(ref)	19	1.00	(ref)	1.00	(ref)	*0.08*	*0.07*	91	1.00	(ref)	1.00	(ref)	40	1.00	(ref)	1.00	(ref)	*0.76*	*0.74*
95–100	29	0.64	(0.39–1.06)	0.80	(0.47–1.36)	19	1.76	(0.84–3.68)	2.21	(0.97–5.03)			90	0.98	(0.73–1.33)	1.19	(0.86–1.64)	42	1.36	(0.85-2.18)	1.26	(0.76–2.08)		
>100	54	1.10	(0.69–1.74)	1.94	(1.02–3.67)	21	2.64	(1.20–5.78)	4.29	(1.46–12.59)			112	1.28	(0.94–1.74)	2.17	(1.41–3.31)	40	1.65	(1.00–2.71)	1.34	(0.69–2.61)		
P-trend			*0.45*		*0.02*			*0.02*		*0.01*					*0.09*		*0.0003*			*0.05*		*0.40*		
Waist-to-hip ratio																								
<0.77	47	1.00	(ref)	1.00	(ref)	23	1.00	(ref)	1.00	(ref)	*0.74*	*0.79*	109	1.00	(ref)	1.00	(ref)	43	1.00	(ref)	1.00	(ref)	*0.34*	*0.37*
0.77–0.82	40	0.85	(0.54–1.33)	0.86	(0.55–1.35)	20	0.65	(0.33–1.31)	0.64	(0.32–1.28)			103	0.98	(0.74–1.29)	0.99	(0.75–1.31)	44	1.20	(0.76–1.90)	1.1	(0.68–1.76)		
>0.82	36	0.72	(0.44–1.17)	0.75	(0.46–1.25)	16	0.52	(0.24–1.12)	0.48	(0.22–1.04)			81	0.81	(0.59–1.11)	0.84	(0.61–1.16)	35	0.96	(0.58–1.57)	0.8	(0.47–1.34)		
P-trend			*0.19*		*0.27*			*0.10*		*0.07*					*0.19*		*0.30*			*0.84*		*0.36*		

[1]Model 1 was adjusted for age at diagnosis, time between exposure measurement and diagnosis, Scarff-Bloom-Richardson (SBR) grade of the tumor (I/II/III), TNM stage (I/II/III), histological subtype (ductal/lobular/mixed/other), menopausal status at diagnosis, age of menopause, use of hormonal treatment of menopause (current/past/never/missing/pre-menopause), use of oral contraceptive (ever/never), number of biological children (0/1/2/3/>3), history of benign breast disease (yes/no), family history of breast cancer (yes/no), smoking status (current smoker/former smoker/never smoker), education level (undergraduate/0–2 years post-graduation/3–4 years post-graduation/≥5 years post-graduation), diabetes (yes/no), and total physical activity (MET h/week) at first questionnaire. Model 1 was also stratified on year of diagnosis (1995–1999/2000–2004/2005-2008).[2]Model 2 was adjusted on waist circumference when BMI was the exposure, and adjusted on BMI for other anthropometric measurements. [3]Deaths (all causes). [4]Second cancer event or death from any cause.
Abbreviations: OS: overall survival; iDFS: invasive disease free survival; HR: hazard ratio; CI: confidence interval; BMI: body mass index.

Table 5. Associations between anthropometric variables before diagnosis and overall mortality and iDFS after breast cancer according to year of diagnosis in the E3N cohort

	OS												iDFS										
	1995–1999 ($N = 935$)					2000–2008 ($N = 2225$)					*P-interaction*		1995–1999 ($N = 935$)					2000–2008 ($N = 2225$)					*P-interaction*	
		Model 1[1]		Model 2[2]			Model 1[1]		Model 2[2]		M1	M2		Model 1[1]		Model 2[2]			Model 1[1]		Model 2[2]		M1	M2
	Events[3]	HR	95% CI	HR	95% CI	Events[4]	HR	95% CI	HR	95% CI			Events[3]	HR	95% CI	HR	95% CI	Events[4]	HR	95% CI	HR	95% CI		
BMI (kg/m^2)																								
5 kg/m^2	145	1.03	(0.80–1.33)	1.09	(0.72–1.65)	141	0.95	(0.75–1.21)	0.96	(0.64–1.42)	*0.15*	*0.14*	289	1.05	(0.87–1.26)	1.11	(0.82–1.50)	331	1.02	(0.88–1.19)	0.99	(0.77–1.28)	*0.60*	*0.60*
<25	99	1.00	(ref)	1.00	(ref)	94	1.00	(ref)	1.00	(ref)	*0.44*	*0.43*	206	1.00	(ref)	1.00	(ref)	216	1.00	(ref)	1.00	(ref)	*0.44*	*0.43*
25–30	33	1.06	(0.69–1.62)	1.09	(0.65–1.84)	41	1.03	(0.70–1.52)	1.02	(0.63–1.64)			67	1.17	(0.87–1.57)	1.26	(0.88–1.82)	98	1.16	(0.90–1.48)	1.1	(0.82–1.49)		
≥30	13	1.19	(0.58–2.45)	1.54	(0.59–4.03)	6	0.68	(0.29–1.60)	0.66	(0.23–1.94)			16	1.12	(0.64–1.96)	1.32	(0.64–2.73)	17	0.83	(0.50–1.39)	0.74	(0.39–1.43)		
P-trend			*0.62*		*0.44*			*0.58*		*0.66*					*0.38*		*0.27*			*0.91*		*0.77*		
Waist circumference (cm)																								
<74	54	1.00	(ref)	1.00	(ref)	40	1.00	(ref)	1.00	(ref)	*0.41*	*0.40*	118	1.00	(ref)	1.00	(ref)	96	1.00	(ref)	1.00	(ref)	*0.59*	*0.59*
74–80	51	1.17	(0.78–1.76)	1.15	(0.75–1.76)	49	1.24	(0.80–1.91)	1.23	(0.78–1.94)			100	1.06	(0.80–1.40)	1.02	(0.76–1.37)	104	1.17	(0.88–1.55)	1.2	(0.89–1.62)		
>80	40	1.00	(0.63–1.60)	0.95	(0.52–1.74)	52	0.90	(0.57–1.43)	0.89	(0.48–1.62)			71	1.00	(0.72–1.39)	0.90	(0.59–1.40)	131	1.20	(0.90–1.60)	1.29	(0.88–1.90)		
P-trend			*0.99*		*0.88*			*0.50*		*0.59*					*0.99*		*0.67*			*0.26*		*0.21*		
Hip circumference (cm)																								
<95	53	1.00	(ref)	1.00	(ref)	34	1.00	(ref)	1.00	(ref)	*0.02*	*0.02*	105	1.00	(ref)	1.00	(ref)	90	1.00	(ref)	1.00	(ref)	*0.46*	*0.44*
95–100	33	0.68	(0.43–1.08)	0.81	(0.50–1.32)	48	1.63	(1.03–2.58)	1.92	(1.18–3.13)			91	0.91	(0.68–1.22)	0.96	(0.70–1.32)	106	1.35	(1.01–1.80)	1.48	(1.09–2.00)		
>100	59	1.46	(0.95–2.23)	2.27	(1.23–4.20)	59	1.60	(1.01–2.53)	2.43	(1.33–4.42)			93	1.27	(0.92–1.73)	1.46	(0.93–2.28)	135	1.48	(1.11–1.97)	1.87	(1.28–2.72)		
P-trend			*0.04*		*0.005*			*0.08*		*0.01*					*0.12*		*0.09*			*0.01*		*0.002*		
Waist-to-hip ratio																								
<0.77	63	1.00	(ref)	1.00	(ref)	44	1.00	(ref)	1.00	(ref)	*0.65*	*0.66*	128	1.00	(ref)	1.00	(ref)	95	1.00	(ref)	1.00	(ref)	*0.28*	*0.25*
0.77–0.82	43	0.85	(0.57–1.27)	0.84	(0.56–1.26)	47	0.81	(0.52–1.24)	0.81	(0.52–1.24)			92	0.96	(0.73–1.27)	0.95	(0.72–1.26)	129	1.25	(0.95–1.65)	1.24	(0.94–1.63)		
>0.82	39	0.95	(0.61–1.48)	0.94	(0.60–1.48)	50	0.69	(0.44–1.08)	0.69	(0.44–1.10)			69	1.02	(0.75–1.39)	1.00	(0.73–1.38)	107	0.86	(0.64–1.15)	0.83	(0.61–1.13)		
P-trend			*0.76*		*0.72*			*0.11*		*0.12*					*0.92*		*0.97*			*0.18*		*0.14*		

[1]Model 1 was adjusted for age at diagnosis, time between exposure measurement and diagnosis, Scarff–Bloom–Richardson (SBR) grade of the tumor (I/II/III), estrogen receptors status (positive/negative/missing), progesterone receptors status (positive/negative/missing),TNM stage (I/II/III), histological subtype (ductal/lobular/mixed/other), menopausal status at diagnosis, age of menopause, use of hormonal treatment of menopause (current/past/never/missing/premenopause), use of oral contraceptive (ever/never), number of biological children (0/1/2/3/>3), history of benign breast disease (yes/no), family history of breast cancer (yes/no), smoking status (current smoker/former smoker/never smoker), education level (undergraduate/0–2 years postgraduation/3–4 years postgraduation/≥5 years postgraduation), diabetes (yes/no) and total physical activity (MET h/week) at baseline questionnaire. [2] Model 2 was adjusted on waist circumference when BMI was the exposure, and adjusted on BMI for other anthropometric measurements. [3]Deaths (all causes). [4]Second cancer event or death from any cause.

Abbreviations: OS: overall survival; iDFS: invasive disease free survival; HR: hazard ratio; CI: confidence interval; BMI: body mass index.

No significant heterogeneity was observed by ERPR status in HC associations although the association with OS seemed stronger in ER−PR− than in ER + PR+ (Model 2: ER + PR+ $HR_{>100 vs < 95\ cm} = 1.94$, CI = 1.02–3.67, $P_{trend} = 0.02$; ER−PR− $HR_{>100 vs < 95\ cm} = 4.29$, CI = 1.46–12.59, $P_{trend} = 0.01$ − $P_{interaction} = 0.07$) (Table 4).

When stratifying analyses according to year of diagnosis (Table 5), we observed a significant interaction for the association between HC and OS ($P_{interaction} = 0.02$). Although going in the same direction, associations were stronger in cases diagnosed in 2000 or after compared to cases diagnosed in 1995–1999 (Model 2, 1995–1999, OS: $HR_{95–100 vs < 95\ cm} = 0.81$, CI = 0.50–1.32, $HR_{>100 vs < 95\ cm} = 2.27$, CI = 1.23–4.20, $P_{trend} = 0.005$; 2000–2008, OS: $HR_{95–100 vs < 95\ cm} = 1.92$, CI = 1.18–3.13, $HR_{>100 vs < 95\ cm} = 2.43$, CI = 1.33–4.42, $P_{trend} = 0.01$). The associations seem also stronger with iDFS although the interaction was not statistically significant.

No statistically significant interaction with menopausal status at diagnosis was observed (Supporting Information Table 1), although our population was mostly postmenopausal and very few events were identified in premenopausal cases.

Excluding women with BMI < 18.5 kg/m^2 in sensitivity analyses did not change the associations between HC and OS, BCSS or iDFS. Similarly, the associations between HC and OS, BCSS and iDFS were of the same magnitude when analyses were restricted to women whose last available BMI was within the 2 years before diagnosis, or to women whose last available BMI was more than one year before diagnosis. Excluding women whose second cancer event had not been validated by a pathological report did not modify the association between HC and iDFS. Lastly, excluding breast cancer cases diagnosed during the last 5 years of follow-up did not alter the findings (data not shown).

Discussion

In this prospective cohort of relatively lean women, BMI, WC and WHR were not associated with survival after breast cancer. However, women with a prediagnostic HC > 100 cm were at increased risk of death (from all causes and from breast cancer) and second invasive cancer event, compared to those with HC <95 cm, especially when BMI was adjusted for.

In 15 out of 22 published studies, BMI-defined obesity compared to normal weight was associated with increased risk of death from any cause, and in 14 of them, it was also associated with breast cancer-specific mortality.[5,20] However, overweight, defined as BMI 25–30 kg/m^2, was not associated with all-cause mortality in any individual study, and the meta-analysis showed a modest increase in mortality (OS: $RR_{overweight\ VS\ normal} = 1.07$ (1.02–1.12)).[5] Thus, the absence of an association between BMI and survival in our study could be explained by the low number of obese women (average BMI: 23.7 kg/m^2, 6% of obese women), and is in agreement with the no or modest associations observed between overall adiposity and survival in the overweight (25–30 kg/m^2) BMI range. Regarding the association between prediagnostic BMI and risk of breast cancer recurrence, reports in the literature were inconsistent, with either positive[21,22] or null[16,23,24] associations.

There were only two previous studies on WC in relation to events in breast cancer survivors, and they found no association with survival.[20,25] To our knowledge, only one study[25] investigated associations between prediagnostic HC and risk of death after breast cancer, on a reduced number of postmenopausal women ($n = 698$; 56 deaths), and reported a nonstatistically significant increase in risk of death. Postdiagnostic HC was not associated with overall survival in two studies.[26,27]

Our results regarding stage of disease showed no interaction or overlapping confidence intervals, and are consistent with existing data. Some studies suggested that the associations of obesity with breast cancer were either stronger or similar among early stage cancer cases, regardless of the time obesity was assessed.[16,28–30] Thus, Majed *et al.*[29] hypothesized that adiposity would play a stronger role in prognosis when other prognostic factors are more favorable.

In published meta-analyses the ER status did not modify the associations between adiposity and breast cancer survival,[5,31] although in one meta-analysis[5] prediagnostic BMI was associated with total and breast cancer mortality only in hormone receptor positive cases.

The literature regarding menopausal status at diagnosis is conflicting, however, two recent meta-analyses concluded that no significant difference was observed in the association between prediagnosis BMI and total and breast cancer-specific mortality between pre and postmenopausal women.[5,31]

Excess adiposity has been associated with several metabolic and hormonal dysregulations that involves sex hormones, insulin and insulin-like growth factors or inflammation pathways and adipocytokines.[32] Evidence toward mechanisms involving insulin was considered the strongest by Niraula and Goodwin.[31,33] However, central adiposity (high WC) is usually more strongly correlated with insulin levels than HC,[34] and our data showed little association of WC with survival. Gluteo-femoral/subcutaneous adiposity, for which HC is a marker,[35,36] is characterized by the secretion of leptin,[34,37,38] an adipocytokine with pro-angiogenic and anti-apoptotic properties.[39] Interestingly, hyperleptinaemia has already been related to poor prognosis after breast cancer.[40] However, further investigation is needed regarding properties of the gluteo-femoral adipose tissue and its secreted products.[36]

Strengths of our study include the prospective design of the E3N cohort study, with regularly updated information, which allowed us to collect anthropometric data from women before their cancer diagnosis, avoiding potential recall bias caused by retrospective assessment at cancer diagnosis. Moreover, first breast cancer cases, and most second events were confirmed by pathological reports, and detailed tumor characteristics were extracted from the records.

However, the E3N cohort study was not originally designed to study survival. Thus, compared to data from clinical studies, some information on tumor characteristics and treatments were incomplete or missing. As the follow-up period for this study lasted from 1995 to 2011, cancer treatments have evolved, as well as routine evaluation of predictive and prognostic factors such as HER2 status. For this reason, we chose to stratify all our analyses by periods of diagnosis. Another limitation is that anthropometric measurements were not clinically assessed, but self-reported. However, a validation study[18] in a subset of the E3N cohort showed high correlation coefficients (>0.80) between weight, height, hip, waist, bust circumferences and BMI measured by a technician, and those measured by the women. Lastly, the low number of BMI-defined obese women and few events in those women limited the study of the association between obesity and survival.

Conclusions

In conclusion, HC was associated with poorer survival after breast cancer in a population of mostly normal-weight French women, whereas BMI-measured overall adiposity was not. This suggests that overall adiposity, at overweight level, does not influence survival and underlines the interest of going beyond BMI when studying anthropometry with regards to breast cancer survival. Thus, we recommend that further studies consider various anthropometric measurements in order to provide complete information that will help to understand the mechanisms underlying associations between adiposity and survival.

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References

1. Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer* 2015; 136:E359–E386.
2. Coleman MP, Quaresma M, Berrino F, et al. Cancer survival in five continents: a worldwide population-based study (CONCORD). *Lancet Oncol* 2008; 9:730–56.
3. Soerjomataram I, Louwman MW, Ribot JG, et al. An overview of prognostic factors for long-term survivors of breast cancer. *Breast Cancer Res Treat* 2008; 107:309–30.
4. Cianfrocca M, Goldstein LJ. Prognostic and predictive factors in early-stage breast cancer. *Oncologist* 2004; 9:606–16.
5. Chan DS, Vieira AR, Aune D, et al. Body mass index and survival in women with breast cancer-systematic literature review and meta-analysis of 82 follow-up studies. *Ann Oncol* 2014; 25: 1901–14.
6. World Cancer Research Fund International/ American Institute for Cancer Research. Continuous update project report: diet, nutrition, physical activity, and breast cancer survivors, 2014.
7. James FR, Wootton S, Jackson A, et al. Obesity in breast cancer—what is the risk factor? *Eur J Cancer* 2015; 51:705–20.
8. Leitzmann MF, Moore SC, Koster A, et al. Waist circumference as compared with body-mass index in predicting mortality from specific causes. *PLoS One* 2011; 6:e18582
9. Pischon T, Boeing H, Hoffmann K, et al. General and abdominal adiposity and risk of death in Europe. *N Engl J Med* 2008; 359:2105–20.
10. Harding JL, Shaw JE, Anstey KJ, et al. Comparison of anthropometric measures as predictors of cancer incidence: a pooled collaborative analysis of 11 Australian cohorts. *Int J Cancer* 2015; 137: 1699–708.
11. Clavel-Chapelon F. Cohort profile: the French E3N cohort study. *Int J Epidemiol* 2015; 44: 801–9.
12. Hudis CA, Barlow WE, Costantino JP, et al. Proposal for standardized definitions for efficacy end points in adjuvant breast cancer trials: the STEEP system. *J Clin Oncol* 2007; 25:2127–32.
13. Ewertz M, Machado SG, Boice JD, Jr., et al. Endometrial cancer following treatment for breast cancer: a case-control study in Denmark. *Br J Cancer* 1984; 50:687–92.
14. Pukkala E, Kyyronen P, Sankila R, et al. Tamoxifen and toremifene treatment of breast cancer and risk of subsequent endometrial cancer: a population-based case-control study. *Int J Cancer* 2002; 100:337–41.
15. Sanchez L, Lana A, Hidalgo A, et al. Risk factors for second primary tumours in breast cancer survivors. *Eur J Cancer Prev* 2008; 17:406–13.
16. Kroenke CH, Chen WY, Rosner B, et al. Weight, weight gain, and survival after breast cancer diagnosis. *J Clin Oncol* 2005; 23:1370–8.
17. Fagherazzi G, Chabbert-Buffet N, Fabre A, et al. Hip circumference is associated with the risk of premenopausal ER-/PR-breast cancer. *Int J Obes (Lond)* 2012; 36:431–9.
18. Gourgou-Bourgade S, Cameron D, Poortmans P, et al. Guidelines for time-to-event endpoint definitions in breast cancer trials: results of the DATECAN initiative (Definition for the assessment of time-to-event endpoints in CANcer trials). *Ann Oncol* 2015; 26:873–9.
19. World Health Organization. Obesity: preventing and managing the global epidemic: report of a WHO consultation on obesity, geneva, 3–5 June 1997, 1998.
20. Kwan ML, John EM, Caan BJ, et al. Obesity and mortality after breast cancer by race/ethnicity: the California breast cancer survivorship consortium. *Am J Epidemiol* 2014; 179:95–111.
21. Kamineni A, Anderson ML, White E, et al. Body mass index, tumor characteristics, and prognosis following diagnosis of early-stage breast cancer in a mammographically screened population. *Cancer Causes Control* 2013; 24:305–12.
22. Loi S, Milne RL, Friedlander ML, et al. Obesity and outcomes in premenopausal and postmenopausal breast cancer. *Cancer Epidemiol Biomarkers Prev* 2005; 14:1686–91.
23. Caan BJ, Kwan ML, Hartzell G, et al. Pre-diagnosis body mass index, post-diagnosis weight change, and prognosis among women with early stage breast cancer. *Cancer Causes Control* 2008; 19:1319–28.
24. Kwan ML, Chen WY, Kroenke CH, et al. Pre-diagnosis body mass index and survival after breast cancer in the after breast cancer pooling project. *Breast Cancer Res Treat* 2012; 132: 729–39.
25. Zhang S, Folsom AR, Sellers TA, et al. Better breast cancer survival for postmenopausal women who are less overweight and eat less fat. The Iowa women's health study. *Cancer* 1995; 76: 275–83.
26. Abrahamson PE, Gammon MD, Lund MJ, et al. General and abdominal obesity and survival among young women with breast cancer. *Cancer Epidemiol Biomarkers Prev* 2006; 15:1871–7.
27. Goodwin PJ, Ennis M, Pritchard KI, et al. Insulin- and obesity-related variables in early-stage breast cancer: correlations and time course of prognostic associations. *J Clin Oncol* 2012; 30: 164–71.
28. Dal Maso L, Zucchetto A, Talamini R, et al. Effect of obesity and other lifestyle factors on mortality in women with breast cancer. *Int J Cancer* 2008; 123:2188–94.
29. Majed B, Moreau T, Senouci K, et al. Is obesity an independent prognosis factor in woman breast cancer? *Breast Cancer Res Treat* 2008; 111: 329–42.
30. Senie RT, Rosen PP, Rhodes P, et al. Obesity at diagnosis of breast carcinoma influences duration of disease-free survival. *Ann Intern Med* 1992; 116:26–32.
31. Niraula S, Ocana A, Ennis M, et al. Body size and breast cancer prognosis in relation to hormone receptor and menopausal status: a meta-analysis. *Breast Cancer Res Treat* 2012; 134: 769–81.
32. IOM (Institute of Medicine). *The role of obesity in cancer survival and recurrence: workshop summary*. Washington, DC: The National Academies Press, 2012.
33. Goodwin PJ. Commentary on: "Effect of obesity on survival in women with breast cancer: systematic review and meta-analysis" (Melinda Protani, Michael Coory, Jennifer H. Martin). *Breast Cancer Res Treat* 2010; 123:637–40.
34. Hocking S, Samocha-Bonet D, Milner KL, et al. Adiposity and insulin resistance in humans: the

role of the different tissue and cellular lipid depots. *Endocr Rev* 2013; 34:463–500.
35. Cornier MA, Despres JP, Davis N, et al. Assessing adiposity: a scientific statement from the American Heart Association. *Circulation* 2011; 124:1996–2019.
36. Manolopoulos KN, Karpe F, Frayn KN. Gluteofemoral body fat as a determinant of metabolic health. *Int J Obes (Lond)* 2010; 34:949–59.
37. Montague CT, Prins JB, Sanders L, et al. Depot- and sex-specific differences in human leptin mRNA expression: implications for the control of regional fat distribution. *Diabetes* 1997; 46:342–7.
38. Van Harmelen V, Reynisdottir S, Eriksson P, et al. Leptin secretion from subcutaneous and visceral adipose tissue in women. *Diabetes* 1998; 47: 913–7.
39. Delort L, Rossary A, Farges MC, et al. Leptin, adipocytes and breast cancer: focus on inflammation and anti-tumor immunity. *Life Sci* 2015; 140:37–48.
40. Ando S, Catalano S. The multifactorial role of leptin in driving the breast cancer microenvironment. *Nat Rev Endocrinol* 2012; 8: 263–75.