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Given breast cancer, does breast size matter? *Data from a prospective breast cancer cohort*

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Given breast cancer, does breast size matter?

Abstract

Purpose: Body mass index (BMI), waist-to-hip ratio (WHR) and tumor characteristics affect disease-free survival. Larger breast size may increase breast cancer risk but its influence on disease-free survival is unclear. The purpose of this study was to elucidate whether breast size independently influenced disease-free survival in breast cancer patients. *Methods:* Body measurements were obtained pre-operatively from 772 breast cancer patients in a population-based ongoing cohort from southern Sweden. The research nurse measured breast volumes with plastic cups used by plastic surgeons doing breast reductions. Clinical data were obtained from patient charts and pathology reports. *Results:* Patients with a BMI≥25kg/m^2 had larger tumors (P<0.001) and more axillary nodal involvement (P=0.030). Patients with a WHR>0.85 had larger tumors (P=0.013), more advanced histological grade (P=0.0016), and more axillary nodal involvement (P=0.012). Patients with right+left breast volume ≥850mL were more likely to have larger tumor sizes (P=0.018), more advanced histological grade (P=0.031), and more axillary nodal involvement (P=0.025). There were 62 breast cancer events during the 7-year follow-up. Breast volume ≥850mL was associated with shorter disease-free survival (P=0.004) and distant metastasis-free survival (P=0.001) in patients with estrogen receptor (ER) positive tumors independent of other anthropometric measurements and age. In patients with ER-positive tumors, breast size was an independent predictor of shorter disease-free (HR 3.64; 95%CI 1.42-9.35) and distant metastasis-free survival (HR 6.33; 95%CI 1.36-29.43), adjusted for tumor characteristics, BMI, age, and treatment. *Conclusion:* A simple and cheap anthropometric measurement with standardized tools may help identify a subgroup of patients in need of tailored breast cancer therapy.

Keywords: Breast Cancer, Prognosis, Body Mass Index, Waist-to-Hip Ratio, Breast Size

Given breast cancer, does breast size matter?

Introduction

Over 7000 women out of the nine million Swedish inhabitants are diagnosed with breast cancer every year; 1500 die yearly from their disease(1). The numbers are comparable across the western world, although Sweden has a relatively lower mortality rate compared to several other western countries (2). Under-treatment of breast cancer increases the risk of recurrence, whereas over-treatment subjects patients to unnecessary treatment side-effects. The identification of factors that influence disease-free survival allows for a better tailoring of treatment intensity and treatment modality.

Certain anthropometric factors influence prognosis. A high body mass index (BMI) was associated with a worse prognosis in both pre- and postmenopausal breast cancer patients(3-7). Obese postmenopausal women presented with more axillary involvement and had shorter disease-free survival than leaner patients(5, 8). Whether a high BMI is associated with estrogen receptor (ER) and progesterone receptor (PR) status is unclear. Some(9, 10), but not all(11), studies have suggested an increased proportion of ER-positive breast cancer cells among obese postmenopausal patients compared to leaner patients.

Waist circumference, often used as a measurement of central adiposity, is another anthropometric factor associated with a worse breast cancer prognosis in both pre- and postmenopausal women(12, 13). A large waist circumference was associated with a more advanced histological grade in postmenopausal patients(12) and larger tumor sizes in non-hispanic white premenopausal breast cancer patients, but not in hispanic breast cancer patients(13). In premenopausal breast cancer patients, an association between a high waist-to-hip ratio (WHR) and a worse outcome has been suggested, also after adjustment for BMI(14). For postmenopausal patients, a high WHR was not associated with disease-free survival after adjustment for BMI as reviewed by Harvie *et al.*(14). However, others found WHR to be an

independent prognostic factor even after taking BMI into account(15). A high WHR may be used as a proxy marker for a high testosterone/estrogen ratio and, perhaps more importantly, for insulin resistance and high levels of fasting insulin, pro-insulin, and C-peptide in women(16-18). Hyperinsulinemia may be associated with a worse outcome of early breast cancer(19-21).

Breast size may be associated with more aggressive tumor characteristics at diagnosis in pre- as well as postmenopausal women(22-26). Even though breast size is strongly correlated with BMI(27), only one third of the genes contributing to breast size has been shown to influence BMI(28). Larger breast size was associated with higher IGF-1 levels in young nulliparous women not using oral contraceptives(29). In addition, a large breast size could be used as a predictor of type II diabetes(30), even when adjusting for BMI and WHR. Breast cancer patients with type II diabetes and ER-negative breast cancer had a more than 2-fold higher risk for distant metastasis compared to patients without diabetes, but this was not seen in patients with ER-positive tumors (31).

Studies investigating breast size in relation to breast cancer have often used brassiere cup size as a size measure(24, 28, 32). However, the different manufacturers have incongruous volume measurement for their cup sizes(33). Moreover, cup size does not take rib cage circumference into account(33). Actual breast volume measurement using plastic cups used for measuring breast volume prior to reduction mammoplasties leads to more reproducible results(34), and allows for an evaluation of whether breast volume *per se* has an impact on tumor disposition or growth pattern.

The identification of prognostic factors allows for a better tailoring of treatment. Prognostic factors may also help identify pathophysiological pathways and novel therapeutic modalities. We hypothesize that anthropometric factors can be used as proxy markers for insulin and IGF-1 levels and the estrogen/testosterone ratio, factors that are known to

influence tumor characteristics and survival. The aim of this study was to examine the relationship between anthropometric factors, tumor characteristics, and disease-free survival, and to investigate whether breast size is an independent prognostic factor.

Materials and Methods

Women assessed preoperatively for a primary breast cancer at the Skane University Hospital in Lund, Sweden, were invited to take part in an ongoing prospective study regarding genetic and non-genetic factors that could be associated with breast cancer prognosis. A total of 819 patients were included between October 2002 and June 2010. The patients were invited to participate regardless of ethnic background, age and stage. Those who had been diagnosed and treated for another type of cancer within the past 10 years were not eligible to participate. We excluded 47 pre-treated patients [interstitial laser thermotherapy (n=11 + one uncertain) or neoadjuvant systemic therapy (n=34 + one patient who received treatment for another cancer between the primary surgery and re-operation)]. The original cohort of 819 patients was therefore limited to 772. The study was approved by the Ethics Committee of Lund University.

Written informed consent was collected during the preoperative visit at the Department of Surgery at the Skane University Hospital in Lund. Body measurements and breast volumes were measured at the preoperative visit. All patients filled out a preoperative questionnaire, including questions on birth date, coffee consumption, smoking, alcohol intake, use of exogenous hormones and concomitant medications, and reproductive history. There was no question regarding ethnicity. However, most women included were ethnic Swedes. The pre-operative visit usually took place a few days prior to surgery.

Trained research nurses measured the volume of each breast, with the patient in a sitting position and her arms hanging down, using plastic cups employed by plastic surgeons doing breast reductions and reconstructions. The volume measurements obtained from such cups have been used since 1994 together with a computerized program to prioritize patients on the waiting list for breast reductions at the Department of Plastic and Reconstructive Surgery at Skane University Hospital in Malmö, Sweden. These cups come in the following 11 sizes: 200, 275, 350, 500, 650, 800, 950, 1150, 1325, 1500 and 2000 mL(33). 'Breast volume' was defined as the sum of the volumes of the right and left breast.

A previous report from this cohort identified 850mL as the median breast volume in the 355 first included patients(33). This volume is similar to the median volume among B cup users obtained in an independent cohort(26). Recent studies indicate that the most common cup-size among women is B(32, 33). Breast volume of 850mL was therefore chosen as a cut-off value between small and large breast volume. Central obesity was considered to be present if the WHR was above 0.85 or if the waist circumference exceeded 80 cm (35). We classified patients according to age (<50 years or ≥50 years of age) instead of reported menopausal status. This cut-off was chosen since postmenopausal patients with previous hormone replacement therapy (HRT)-use may have had HRT-induced bleedings and could have been misclassified as premenopausal. Patients who had had their uterus removed before menopause but not their ovaries may also have been misclassified.

Additional baseline information, including type of surgery, sentinel node biopsy, and axillary node dissection, were obtained from each patient's chart. Tumor size, histological type and grade, axillary node involvement, signs of distant metastases, and ER and PR status were obtained from each patient's pathology report. Tumors with >10% positive nuclear staining were considered receptor positive (36). All tumors were analyzed at the Department

of Pathology at Skane University Hospital in Lund. HER-2/neu status was routinely analyzed as of November 2005.

Skane University Hospital in Lund is one of seven hospitals in the South Swedish Health Care Region performing breast cancer surgery. Its catchment area serves almost 300,000 inhabitants. Patients with breast cancer are not referred to other hospitals for surgery, so this study population is population-based. During the same period as this cohort was accrued, there were 1543 patients who went through breast cancer surgery in Lund. The mean age was 61.15 years, ER-status was reported in 91.2% of the patients and PR-status was reported in 90.6% of the patients; 85.7% of the tumors were ER-positive and 69.8% of the tumors were PR-positive. Approximately 50% of the patients in Lund were thus included in this study and were similar to non-included patients with respect to age, ER- and PR-status. Most non-included patients were missed due to lack of available research nurses. Approximately five percent of the patients were missed due to unverified diagnosis at the time of surgery.

The follow-up rates for the breast cancer patients in our cohort who were alive and recurrence-free at each follow-up were as follows for the 1-year, 2-year, 3-year, 5-year, and 7-year follow-up: 98.0%, 95.1%, 92.4%, 94.6%, and 90.8%, respectively.

Statistics

The statistical analysis was performed with the software SPSS 18.0. In the screening detection analysis we chose to exclude women <45 years (n=71), as Lund's screening program for breast cancer previously started at age 45. In the breast size analyses, women who had undergone previous breast operations (n=89) or lacked breast size measurements (n=6) were excluded. BMI, WHR, and waist measurements were not normally distributed. Therefore the variables were either dichotomized or transformed using the natural logarithm. In the survival

analysis, two forms of events were evaluated; any breast cancer event or distant metastases. A breast cancer event was defined as an ipsi-, contralateral-, regional-, or distant metastasis. Patients with *in situ* tumors (n=28) and patients with metastasis detected on the postoperative metastasis screen within three months of inclusion (n=5) were excluded from the survival analysis. After exclusion, there were 62 patients with any type of breast cancer event during the seven-year follow-up, of which 40 had distant metastasis. Breast cancer-free survival was calculated from inclusion to diagnosis of a breast cancer event or distant metastasis prior to June 30 2010, last study follow-up or death due to non-breast cancer related causes. Chi-square analyses were used to investigate categorical variables: pathological tumor size (pT; 1-4 or 2+), pathological axillary lymph node involvement (pN; yes/no) or number of involved lymph nodes (0, 1-3, 4+), and histological grade (I-III or I-II *versus* III) in relation to age and body constitution. Kaplan-Meier was used to calculate disease-free survival. Cox regression was used to obtain adjusted hazard ratios (HR), adjusting for age, pT, lymph node involvement, and histological grade. A *P*-value <0.05 was considered significant. All *P*-values were two-tailed.

Results

The characteristics of the patients are presented in Table 1. Age at breast cancer diagnosis ranged from 25 to 99 years, with a median of 60.4 years. The median breast volume was 1000mL, the median WHR was 0.85 and the median BMI was 24.8. Previous HRT-use among women aged 50 years or older did not differ according to BMI or breast size. Previous HRT use among women aged ≥50 years differed according to WHR, women with a WHR ≤0.85 were more likely to have used HRT than women with a WHR >0.85 [Odds Ratio (OR) 1.75; 95%CI 1.15-2.66].

Tumor characteristics

Tumor characteristics for the 772 women are presented in Table 2. Tumor size, histological grade, axillary nodal involvement, and the proportion of screening detected tumors differed according to age and body constitution.

Disease-free survival in relation to age and anthropometric factors

The median follow-up was 2.94 years (IQR 1.03-4.90 years) in the 739 patients with invasive tumors without distant metastasis detected on the postoperative metastasis screen. Patients younger than 50 years had shorter disease-free survival (P=0.001) and borderline significantly shorter distant metastasis-free survival (P=0.047) compared to older patients (Figure 1a). Patients with a BMI ≥25 kg/m^2 had a non-significantly shorter disease-free and distant metastasis-free survival (Figure 1b). This weak association was seen in both younger and older patients. No association between BMI and disease-free survival in relation to ER-status was observed.

We then studied fat distribution. A WHR >0.85 was associated with shorter disease-free survival (P=0.036) and distant metastasis-free survival (P=0.035; Figure 1c). A WHR >0.85 was associated with shorter distant metastasis-free survival in both age categories but was only significant in patients 50 years or older with a WHR >0.85 (P=0.015). Patients with a waist ≥80 cm had significantly shorter disease-free survival (P=0.042) but only non-significantly shorter distant metastasis-free survival (P=0.088; Figure 1d).

Fifty-eight percent of the study population had breast volume ≥850mL. Breast volume ≥850mL was associated with shorter disease-free survival (P=0.006). After stratification according to ER status, breast volume ≥850mL was associated with shorter disease-free

(*P*=0.004; Figure 2a) and distant metastasis-free survival (*P*=0.001; Figure 2b), in patients with ER-positive, but not ER-negative, tumors.

Multivariate analyses of disease-free survival

In three separate Cox regression models, breast volume ≥850mL predicted disease-free and distant metastasis-free survival better in patients with ER-positive tumors than did BMI, WHR, or waist circumference adjusting for tumor characteristics, age, and endocrine treatment. The highest hazard ratios with large breast size were obtained in the model adjusting for waist circumference, Table 3.

Adding HRT to the model did not materially change the results of any of the models. In all three models, breast volume ≥850mL was the strongest predictor of disease-free survival. Patients with breast volume ≥850mL and ER-positive tumors had shorter disease-free and distant metastasis-free survival compared to patients with smaller breasts, regardless of age, BMI, WHR, and waist circumference. The results remained materially the same after further adjustment for type of surgery (modified radical mastectomy or lumpectomy). Type of surgery was not associated with early breast cancer events (*P*=0.73).

Discussion

The main finding of this study was that breast volume ≥850 mL in women with ER-positive tumors was associated with significantly shorter disease-free survival compared to women with smaller breasts, independent of age, BMI, WHR and waist circumference. Consistent with the findings of earlier studies(22-26), women with larger breasts presented with more aggressive tumor characteristics than women with smaller breasts. In the present study, larger

breast size alone was associated with shorter disease-free survival – regardless of other anthropometric measurements, age, histological grade, and axillary lymph node involvement of the patient.

The results of this study need to be further explored to elucidate the mechanism underlying our finding of an increased risk for an early breast cancer event in women with larger breast size. Investigating fat/gland ratio or mammographic density in this group of women may be of value(27), but has not been part of this study. All body measurements were obtained by trained nurses prior to surgery and subsequent events, minimizing the risk for bias. Since this material is taken from a predominantly Caucasian population it is unclear whether these results are applicable to patients of other ethnicities. Moreover, given that many previous studies were carried out in patient groups with a greater range of BMI than was observed in this study population(3, 9), it is unclear whether the associations found here are linear or would change at more extreme values of BMI. In the multivariate models we chose to include BMI and WHR as linear variables, to minimize residual confounding.

One plausible mechanism for our observation of an association between breast size and prognosis may be increased levels of IGF-1(37). Some studies indicated a clear association between cancer and the insulin/IGF-1 axis(38-41). Three of the studies demonstrated the involvement of these factors in breast cancer(39-41). The meta-analyses showed that higher IGF-1 levels were only associated with risk for ER-positive breast cancer(41). In the follicular phase of the menstrual cycle, IGF-1 levels were positively associated with breast size in young nulligravid women not using oral contraceptives(29). In line with this, Hartmann *et al.* showed that the success rate of breast augmenting estrogen stimulation was dependent on a subsequent increase of IGF-1 concentrations in the women tested(42). Moreover, high IGF-1 levels have been linked to mammographic density in premenopausal women(43). Mammographic density is significantly associated with breast

cancer mortality(44). A larger breast size may thus be a surrogate marker for high IGF-1 levels, which would be of interest when investigating disease-free survival in patients with larger breasts as the IGF-1 receptor (IGF1R) is currently one of the most studied molecular targets in the field of oncology(45). Conversely, the body constitution of women with larger breasts, low to normal BMI and low WHR reflects an estrogenic profile(18, 26, 46), which could impact on tumor growth and hormone receptor status. A recent report from a subset of the current patient cohort, showed that certain androgen receptor (AR) genotypes were associated with significantly larger breast size, but not with increased WHR. These AR genotypes were also significantly associated with shorter disease-free survival (47).

A WHR >0.85 was associated with somewhat shorter disease-free survival and more aggressive tumor characteristics. A high WHR can be an indicator of a number of unfavourable conditions, such as an elevated testosterone/estrogen ratio(17, 48), cortisol surges in response to stress or metabolic issues(17), or hyperinsulinemia(18, 49). Accordingly, hyperinsulinemia-associated (diabetes type II associated) WHR increase could be of importance for breast cancer prognosis. A mouse model showed that visceral fat increased inflammation and elevated aromatase expression in the mammary gland(50). Measurements of circulating androgens, insulin, IGF-1, and cortisol may be beneficial for patients with a high WHR, as it may provide information on which pathway to target during tailored breast cancer treatment. There are currently ongoing trials with metformin(51) and a phase II trial of the nonsteroidal antiandrogen bicalutamide enrolling women with ER-/PR-/AR+ breast cancers (ClinicalTrials.gov Identifier NCT00468715)(51). WHR was not nearly as strongly associated with prognosis as breast volume was in the present study.

Concordant with earlier studies(5), patients in this cohort with a BMI $\geq$25 kg/m^2 had larger tumors. A cut-off at BMI $\geq$30 kg/m^2 generated similar results [data not shown]. No association between BMI $\geq$25 kg/m^2 and hormone receptor status was observed, in contrast to

findings by Enger *et al*.(9). In Enger's study, only 73% of the tumors were ER-positive compared to over 85% in Lund.

In spite of larger tumors in patients with a higher BMI, we found only a non-significant association between obesity and breast cancer prognosis in the current study. This is in contrast to the findings of Petrelli *et al.* in a study of 2852 postmenopausal breast cancer deaths with a 14 year follow-up(8). Furthermore, in the present study, no significant association between BMI and disease-free survival among younger women was observed, as opposed to earlier findings(6). A cut-off at BMI ≥30 kg/m^2 generated similar results [data not shown]. The discrepant results may in part be due to the categorization according to age in the present study as opposed to the categorization according to menopausal status or the shorter follow-up. However, a more likely explanation may be that fat distribution matters more than fat accumulation.

In conclusion, the present study showed significantly shorter disease-free survival for breast cancer patients with ER-positive tumors and breast volume ≥850mL, regardless of age, WHR, waist circumference, and BMI. Our results warrant confirmation in an independent cohort. If confirmed, a simple anthropometric measurement that could rapidly and cheaply be obtained using plastic surgery cups, could yield important prognostic information beyond that obtained through the pathology report and clinical assessment. The results may then need to be taken into account to tailor treatment intensity and modality.

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Figure legends

Fig 1 Kaplan-Meier estimate of the distant metastasis-free survival in relation to age and body constitution.

a) Distant metastasis-free survival in relation to age. The grey line illustrates disease-free survival in patients <50 years, the black line illustrates disease-free survival in patients ≥50 years. Numbers below the figure indicate participants each year at follow-up, the upper line referring to patients <50 years, the lower line referring to patients ≥50 years. (Log-Rank; P=0.047).

b) Distant metastasis-free survival in relation to BMI. The grey line illustrates disease-free survival in patients with BMI <25, the black line illustrates disease-free survival in patients with BMI ≥25. The number of patients in each subgroup is indicated below the graph. (Log-Rank; P=0.075).

c) Distant metastasis-free survival in relation to WHR. The grey line illustrates disease-free survival in patients with WHR ≤0.85, the black line illustrates disease-free survival in patients

with WHR >0.85. Numbers below the figure indicate participants each year at follow-up, upper line referring to WHR ≤0.85, the lower line referring to WHR >0.85. (Log-Rank; *P*=0.035).

d) Distant metastasis-free survival in relation to waist circumference. The grey line illustrates disease-free survival in patients with waist circumference <80 cm, the black line illustrates disease-free survival in patients with waist circumference ≥80 cm. Numbers below the figure indicate participants each year at follow-up, the upper line referring to waist circumference <80 cm, the lower line referring to waist circumference ≥80 cm (Log-Rank; *P*=0.088).

Fig 2 Kaplan-Meier estimate of the disease-free survival and distant metastasis-free survival in relation to breast size.

a) Disease-free survival in patients with ER-positive tumors. The grey line indicates disease-free survival in patients with a breast size <850 mL, the black line indicates disease-free survival in patients with a breast size ≥850 mL. The number of patients in each subgroup is indicated below the graph. (Log-Rank; *P*=0.004).

b) Distant metastases-free survival in patients with ER-positive tumors. The grey line indicates disease-free survival in patients with a breast size <850mL, the black line indicates disease-free survival in patients a breast size ≥850mL. The number of patients in each subgroup is indicated below the graph (Log-Rank; *P*=0.001).

Conflict of interest

The authors declare that they have no conflict of interest.

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Table 1. Patient characteristics.

	All patients, n = 772	Missing	Breast volume <850mL n = 284	Breast volume ≥850mL n = 393
	Median (IQR) or percent		Median (IQR) or percent	Median (IQR) or percent
Age at diagnosis (years)	60.4 (52.3-66.9)	-	57.8 (49.9-64.9)	61.4 (54.2-68.2)
Age at menarche (years)	13.0 (12.0-14.0)	3	13.0 (12.0-14.0)	13.0 (12.0-14.0)
Parous (%)	86.3 %	-	85.9%	87.5%
Parity (no of children)	2 (1-3)	-	2 (1-3)	2 (1-3)
Ever oral contraceptive use (%)	70.9 %	-	78.5%	66.2%
Ever hormone replacement therapy use (%)	45.8 %	2	40.1%	48.1%
Smoking during last week (%)	22.3 %	-	26.1%	18.8%
Height (cm)	165.0 (162.0-170.0)	2	167.0 (162.0-170.0)	165.0 (161.6-169.0)
Weight (kg)	68.6 (61.0-77.0)	3	62.5 (57.0-68.5)	73.5 (66.0-84.0)
BMI (kg/m^2)	24.8 (22.4-28.0)	4	22.5 (20.9-24.3)	26.8 (24.4-30.5)
Total breast volume (mL)*	1000 (650-1500)	95	600 (425-700)	1400 (1000-1825)
Waist-to-hip ratio	0.85 (0.80-0.90)	2	0.81 (0.76-0.86)	0.87 (0.83-0.92)

*Total breast volume was not analyzed for women with previous breast surgeries (n=89). Breast volume was missing for an additional 6 women.

Table 2. Tumor characterstics in relation to age, BMI, WHR, and breast size.

	Number of patients (%) Total number of patients n=772	Age<50 n=151 (%)	Age≥50 n=621 (%)		BMI<25 n=397 (%)	BMI≥25 n=371 (%)		WHR≤0.85 n=404 (%)	WHR>0.85 n=366 (%)		Waist<80 n=209 (%)	Waist≥80 n=561 (%)		Breast size <850mL n=284 (%)	Breast size ≥850mL n=393 (%)	
pT				p = 0.044			p < 0.001			p=0.013			p = 0.071			p = 0.018
In situ	28 (3.6)	0 (0)	28 (4.5)		17 (4.3)	11 (3.0)		11 (2.7)	17 (4.6)		6 (2.9)	22 (3.9)		10 (3.5)	13 (3.3)	
1	539 (69.8)	102 (67.5)	437 (70.4)		298 (75.1)	238 (64.2)		299 (74.0)	239 (65.3)		166 (79.4)	372 (66.3)		214 (75.4)	258 (65.6)	
2	192 (24.9)	46 (30.5)	146 (23.5)		81 (20.4)	110 (29.6)		88 (21.8)	103 (28.1)		35 (16.7)	156 (27.8)		58 (20.4)	114 (29.0)	
3	12 (1.6)	3 (2.0)	9 (1.4)		1 (0.3)	11 (2.8)		5 (1.2)	7 (1.9)		2 (1.0)	10 (1.8)		1 (0.4)	8 (2.0)	
4	1 (0.1)	0	1 (0.2)		0	1 (0.3)		1 (0.2)	0		0	1 (0.2)		1 (0.4)	0	
Missing	0	0	0		0	0		0	0		0	0		0	0	
Histological grade				p = 0.017			p = 0.23			p=0.016			p = 0.015			p = 0.031
I	191 (25.0)	32 (21.3)	159 (25.9)		108 (27.5)	82 (22.3)		115 (28.7)	75 (20.8)		64 (30.8)	126 (22.7)		79 (28.0)	90 (23.3)	
II	382 (50.0)	67 (44.7)	315 (51.3)		187 (47.6)	193 (52.6)		199 (49.6)	183 (50.7)		105 (50.5)	277 (50.0)		138 (48.9)	194 (50.1)	
III	191 (25.0)	51 (34.0)	140 (22.8)		98 (24.9)	92 (25.1)		87 (21.7)	103 (28.5)		39 (18.8)	151 (27.3)		65 (23.0)	103 (26.6)	
Missing	8	1	7		4	4		3	5		1	7		2	6	
Hormone receptor status																
ER+ (%)	647 (86.8)	122 (81.3)	525 (88.2)	p = 0.025	337 (88.5)	306 (85.0)	p = 0.17	349 (88.6)	296 (84.8)	p=0.233	182 (89.2)	463 (85.9)	p = 0.130	244 (88.7)	320 (84.4)	p = 0.13
PR+ (%)	516 (69.3)	105 (70.0)	411 (66.2)	p = 0.83	263 (66.2)	250 (69.4)	p = 0.90	275(69.8)	241 (69.1)	p=0.934	142 (67.9)	374 (66.7)	p = 0.826	198 (72.0)	260 (66.2)	p = 0.35
Missing	27	1	26		16	11		10	17		5	22		9	14	
Nodal involvement				p = 0.28			p = 0.030			p=0.012			p = 0.022			p = 0.025
0 positive nodes	477 (61.8)	85 (56.3)	392 (63.1)		262 (66.0)	213 (57.4)		254 (62.9)	223 (60.9)		147 (70.3)	330 (58.8)		186 (65.5)	236 (60.1)	
1-3 positive nodes	224 (29.0)	49 (32.5)	175 (28.2)		106 (26.7)	116 (31.3)		124 (30.7)	99 (27.0)		49 (23.4)	174 (31.0)		83 (29.2)	113 (28.8)	
≥4 positive nodes	71 (9.3)	17 (11.3)	54 (8.7)		29 (7.3)	42 (11.3)		26 (6.4)	44 (12.0)		13 (6.2)	57 (10.2)		15 (5.3)	44 (11.2)	
Missing	0	0	0		0	0		0	0		0	0		0	0	
Tumor discovery				p = 0.021			p = 0.001			p<0.001			p < 0.001			p < 0.001
Screening detected	429 (61.3)	39 (49.4)	390 (62.8)		196 (55.2)	230 (67.3)		193 (54.2)	235 (68.7)		92 (50.0)	336 (65.4)		126 (50.2)	253 (69.9)	
Not screening detected	271 (38.7)	40 (50.6)	231 (37.2)		159 (44.8)	112 (32.7)		163 (45.8)	107 (31.3)		92 (50.0)	178 (34.6)		127 (49.8)	109 (30.1)	

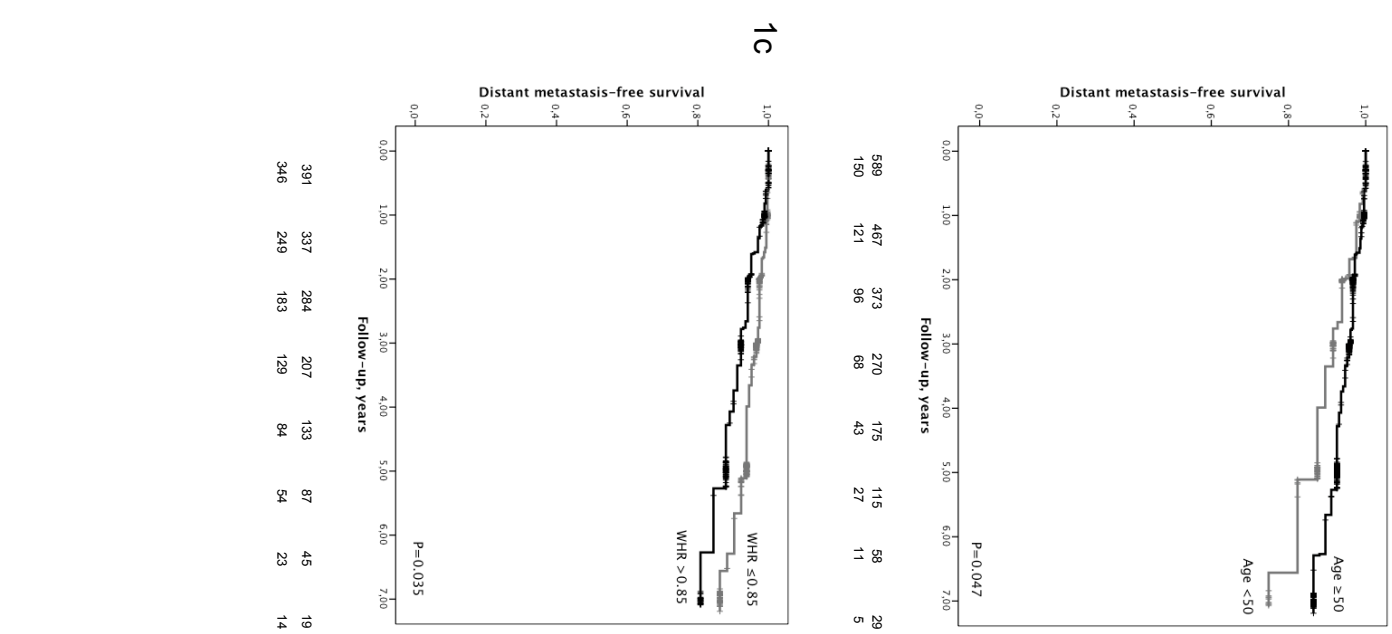
Missing values: BMI four missing, WHR 2 missing, Waist 2 missing; ER & PR 27 missing, Breast size 6 missing and 89 excluded due to previous breast surgeries.

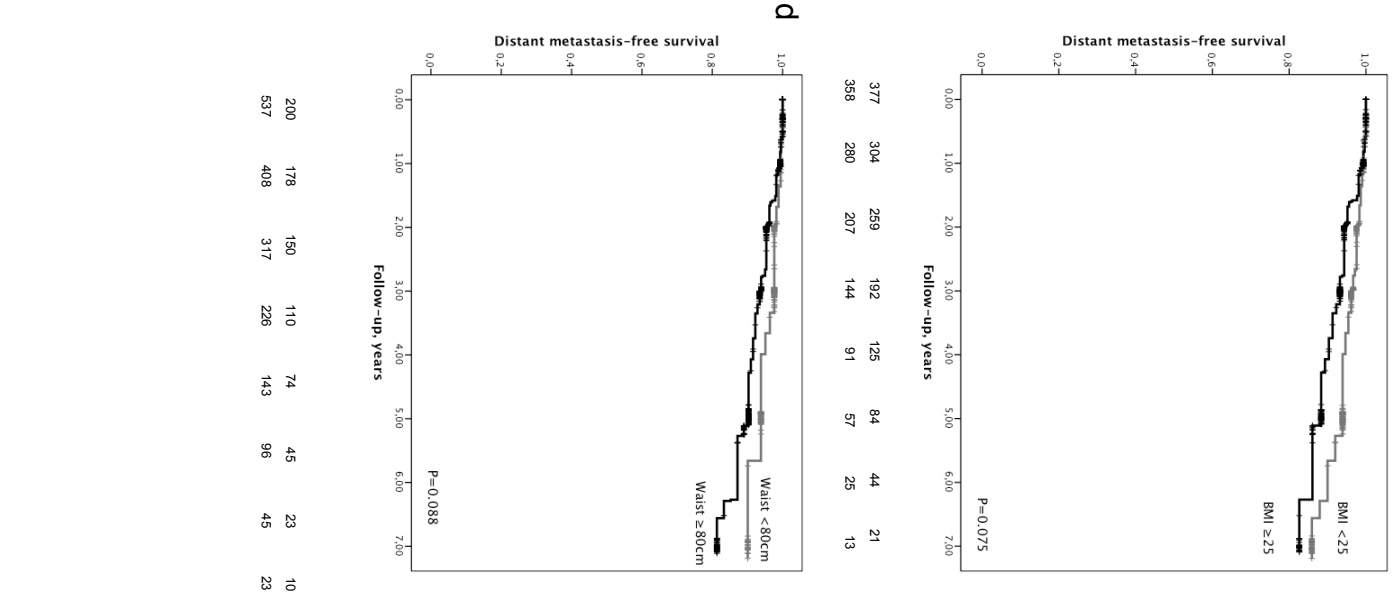
Table 3. Multivariate models of disease-free and distant metastasis-free survival in relation to breast size, adjusted for BMI, WHR, and waist circumference, respectively, in patients with ER-positive tumors.

Disease-free survival adjusted for BMI					**Distant metastasis-free survival**			
		95.0% CI for HR				95.0% CI for HR		
	HR	Lower	Upper	Sig.	HR	Lower	Upper	Sig.
Breast size ≥850mL	**3.64**	**1.42**	**9.35**	**0.007**	**6.33**	**1.36**	**29.43**	**0.019**
Age, years	0.97	0.95	1.00	0.053	0.99	0.96	1.02	0.55
pT 2 or larger	1.72	0.81	3.68	0.16	3.13	1.26	7.74	0.014
pN positive	2.03	0.90	4.57	0.086	2.46	0.88	6.87	0.086
Histological grade III	2.84	1.23	6.53	0.014	3.24	1.25	8.41	0.016
Ln transformed BMI	1.36	0.15	12.00	0.78	2.99	0.23	39.48	0.41
Ever tamoxifen, yes	0.35	0.17	0.72	0.004	0.38	0.16	0.92	0.033
Ever AI* use, yes	0.44	0.20	0.99	0.046	0.53	0.20	1.39	0.20
Disease-free survival adjusted for WHR					**Distant metastasis-free survival**			
		95.0% CI for HR				95.0% CI for HR		
	HR	Lower	Upper	Sig.	HR	Lower	Upper	Sig.
Breast size ≥850mL	**3.81**	**1.50**	**9.68**	**0.005**	**6.96**	**1.47**	**32.95**	**0.014**
Age, years	0.97	0.94	1.00	0.046	0.99	0.96	1.02	0.45
pT 2 or larger	1.73	0.81	3.69	0.16	3.15	1.28	7.77	0.013
pN positive	2.03	0.90	4.57	0.086	2.49	0.89	6.97	0.082
Histological grade III	2.75	1.19	6.39	0.018	2.85	1.07	7.56	0.036
Ln transformed WHR	1.10	0.02	61.41	0.96	2.42	0.012	488.32	0.74
Ever tamoxifen, yes	0.35	0.17	0.72	0.004	0.38	0.16	0.94	0.037
Ever AI* use, yes	0.44	0.20	0.99	0.046	0.53	0.20	1.42	0.21
Disease-free survival adjusted for waist circumference					**Distant metastasis-free survival**			
		95.0% CI for HR				95.0% CI for HR		
	HR	Lower	Upper	Sig.		Lower	Upper	Sig.
Breast size ≥850mL	**3.92**	**1.50**	**10.27**	**0.005**	**6.87**	**1.44**	**32.83**	**0.016**
Age, years	0.97	0.95	1.00	0.045	0.99	0.96	1.02	0.46
pT 2 or larger	1.73	0.81	3.69	0.15	3.16	1.28	7.85	0.013
pN positive	2.08	0.91	4.58	0.085	2.47	0.88	6.95	0.086
Histological grade III	2.77	1.20	6.40	0.017	2.93	1.13	7.60	0.027
Ln transformed waist circumference	0.88	0.06	13.37	0.93	1.88	0.06	56.74	0.72
Ever tamoxifen, yes	0.35	0.17	0.71	0.004	0.37	0.15	0.91	0.030
Ever AI* use, yes	0.44	0.20	0.98	0.045	0.52	0.20	1.38	0.19

AI Aromatase inhibitor

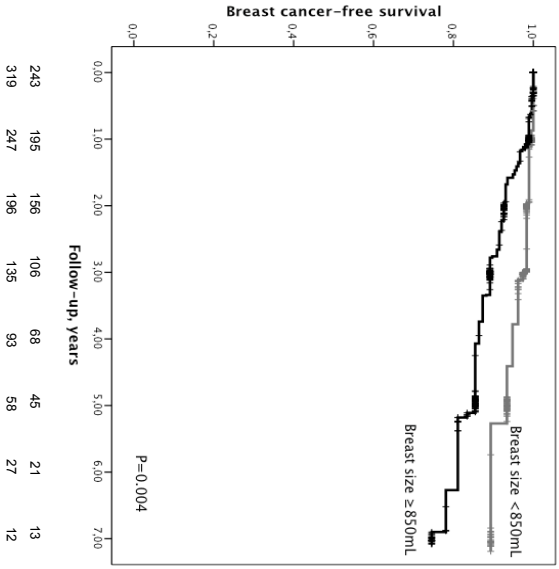
Given breast cancer, does breast size matter?





Given breast cancer, does breast size matter?

2b



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