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Impact of Body Mass Index on Prognostically Relevant Breast Cancer Tumor Characteristics

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Keywords

Breast cancer · Body mass index · Tumor size · Prognostic factors · Tumor detection

Schlüsselwörter

Mammakarzinom · Body-Mass-Index · Tumorgröße · Prognosefaktoren · Tumordetektion

Summary

Background: This study analyzes the association of body mass index (BMI) and prognostically relevant breast cancer (BC) characteristics in a country that has been rather spared of the global obesity epidemic. **Patients and Methods:** Based on 20-year data (1999–2009, n = 1,414) of the prospective relational BC database of the University Hospital Basel, Switzerland, the associations between BMI, tumor size and stage, histological subtype, grading, hormonal receptor status, HER2 status and 'triple-negative' status were evaluated. Multivariate analysis considered BMI and patient's age. **Results:** The association between increasing BMI and the above-mentioned variables were as follows (results described in each case: Beta-coefficient or odds ratio, 95% confidence interval, p value): tumor size, (1) entire cohort: 0.03 (0.01–0.05), p < 0.001, (2) tumor found by self-palpation: 0.05 (0.03–0.07), p < 0.001, (3) tumor found by radiological examination: 0.03 (0–0.07), p = 0.044; advanced TNM stage: 1.16 (1.02–1.31), p = 0.022; histological subtype: 1.04 (0.89–1.22), p = 0.602; unfavorable grading: 1.11 (1.00–1.25), p = 0.057; positive estrogen receptor status: 0.95 (0.83–1.09), p = 0.459; positive HER2 status: 0.92 (0.74–1.15), p = 0.467; presence of a 'triple-negative' carcinoma: 1.19 (0.93–1.52), p = 0.165. Consideration of only postmenopausal BC patients (n = 1,063) did attenuate the results, but did not change the direction of the associations with BMI. **Conclusion:** BMI was positively associated with TNM stage, grading and tumor size for tumors that were found by self-detection, as well as for those lesions detected by radiological breast examinations.

Zusammenfassung

Hintergrund: Die Studie analysiert, inwieweit der Body-Mass-Index (BMI) Einfluss auf prognostisch relevante klinische und pathologische Mammakarzinom-Merkmale in einem Land hat, in dem die global zu beobachtende «obesity epidemic» bisher ausgeblieben ist. **Patienten und Methoden:** Aus den Daten der Mammakarzinom-Datenbank der Basler Universitäts-Frauenklinik, welche einen 20-Jahres-Zeitraum dokumentiert (1990–2009, 1459 Patientinnen), wurde der Einfluss des BMI auf folgende prognostisch relevante Variablen untersucht: Tumorgröße und -stadium, histologischer Subtyp, Grading, Hormonrezeptorstatus, HER2-Status, «triple-negativer»-Status. Das multivariate Berechnungsmodell berücksichtigte neben dem BMI das Alter der Patientin. **Ergebnisse:** Die Korrelationen zwischen steigendem BMI und den oben genannten Faktoren waren wie folgt (Angaben jeweils: Odds ratio (OR), 95% Konfidenzintervall, p-Wert): Tumorgröße, a) alle Patientinnen: 0,03 (0,01–0,05), p < 0,001, b) Tumor von Patientin selbst bemerkt/getastet: 0,05 (0,03–0,07), p < 0,001, c) Tumor durch bildgebende Verfahren entdeckt: 0,03 (0–0,07), p = 0,044; höheres TNM-Stadium: 1,16 (1,02–1,31), p = 0,022; histologischer Subtyp: 1,04 (0,89–1,22), p = 0,602; ungünstiges Grading: 1,11 (1,00–1,25), p = 0,057; positiver Östrogenrezeptorstatus: 0,95 (0,83–1,09), p = 0,459; positiver HER2-Status: 0,92 (0,74–1,15), p = 0,467; Vorliegen eines «triple-negativen» Karzinoms: 1,19 (0,93–1,52), p = 0,165. Nur postmenopausale Patientinnen berücksichtigend (n = 1063), änderten sich die Ergebnisse nur marginal. **Schlussfolgerungen:** Mit steigendem BMI wurde eine positive Korrelation zu einem höheren TNM-Stadium, einem ungünstigen Grading und der Tumorgröße (sowohl für die Fälle, bei denen der Tumor von den Patientinnen selbst bemerkt/getastet wurde, als auch für die Tumoren, die mit radiologischen Verfahren detektiert wurden) gefunden.

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Introduction

In most epidemiological studies, obesity is associated with an increased risk of postmenopausal breast cancer (BC), while an inverse relationship is observed in premenopausal women. In addition, being obese has been shown to influence BC prognosis adversely [1–3]. It has been suggested that larger tumor size, more advanced stage and grade of the tumor at diagnosis [4] could explain in part this bad outcome. The findings of several studies are in accordance with this hypothesis [5, 6]; however, others are not [7].

Unfavorable tumor characteristics may also explain the worse outcome of obese BC patients [2]. Furthermore, histological BC subtypes may differ in their associations with established BC risk factors [8–11]. The few studies exploring the association between body size and aggressive triple-negative BC (TNBC) reported largely inconsistent results [12]. On the other hand, evidence of a positive association between body size and estrogen receptor (ER)-positive BC is quite consistent [13–15]. For example, Phipps et al. [12] in their cohort study including 155,723 women enrolled in the Women's Health Initiative found an increased risk of TNBC (odds ratio (OR) = 1.35; 95% confidence interval (CI): 0.92–1.99) and ER-positive carcinomas (OR = 1.39; 95% CI: 1.22–1.58) for women in the highest, compared with the lowest, body mass index (BMI) quartile. Even though the ER-positive BC subtype has a rather good prognosis, obesity in postmenopausal women may result in more biologically aggressive ER-positive tumors [16, 17].

To evaluate some of these controversial issues, we used data from a Swiss prospective BC database. Data from Switzerland is particularly interesting since the prevalence of overweight and obesity are low when compared to international statistics, and it seems, so far, that Switzerland, similar to a few other countries such as Italy or Sweden, has been spared from the globally observed 'obesity epidemic' [18–20]. For the present analysis, we evaluated the impact of BMI and age on the following prognostically relevant factors: tumor size (tumor detected by self-palpation or by radiological examination) and stage, histological subtype, grading, hormonal receptor status, HER2 status, 'triple-negative' status (hormonal receptor and HER2 status negative) and the risk score defined at the St. Gallen Expert Consensus Meeting in 2007 [21].

Patients and Methods

Based on the prospective relational web-based Basel Breast Cancer Database (BBCD) of the University Women's Hospital Basel (Basel, Switzerland), which documents all newly diagnosed and treated invasive breast carcinomas at this institution over a 20-year period (1990–2009, 1,459 patients), we evaluated the impact of BMI on prognostically relevant tumor characteristics of BC patients.

The predictor variable of our study was BMI. This variable was calculated using the following standard formula: body weight (kg)/height (m^2). In this study, we exclusively used directly measured BMI data taken at the time of initial BC diagnosis. No BMI information was available for only 44 women of the entire BBCD cohort; thus, our study cohort comprised 1,415 patients. Besides age at initial diagnosis, the following clinicopathological features/characteristics were evaluated: tumor categories and stage according to the current American Joint Committee on Cancer (AJCC)/International Union Against Cancer (UICC) TNM classification [22, 23]; histological subtype; grading; hormonal receptor status (ER status and progesterone receptor (PR) status); HER2 status (HER2 has routinely been assessed for all patients since 2002 (n = 665) and was available for 660 patients (46.6% of the entire study cohort)); TNBC; and risk score (as defined at the St. Gallen Expert Consensus Meeting in 2007) [21].

In addition, we considered the method of tumor detection, and evaluated 3 different methods: self-detection, clinical breast examination and radiological breast examination including mammography and sonography.

Table 1. Basel Breast Cancer Database 1990–2009: clinicopathological characteristics of 1415 patients

Characteristic	
Age at diagnosis, median in years (range)	61 (26–95)
BMI median (range)	24.7 (14.3–53.3)
< 18.5, n (%)	38 (2.7)
18.5–24.9, n (%)	712 (50.3)
25–29.9, n (%)	425 (30.0)
≥ 30, n (%)	240 (17.0)
Tumor size, median in mm (range)	20 (0–220)
T1, n (%)	717 (50.7)
T2, n (%)	523 (37.0)
T3, n (%)	80 (5.7)
Non-inflammatory T4, n (%)	70 (5.0)
Inflammatory carcinoma (no tumor size recorded), n (%)	23 (1.6)
Missing, n	2
TNM stage, n (%)	
I	527 (37.2)
II	558 (39.5)
III	249 (17.6)
IV	81 (5.7)
Histological subtype, n (%)	
Ductal invasive	1097 (78.4)
Lobular invasive	197 (14.1)
Other types	106 (7.5)
Missing, n	15
Grading, n (%)	
G1/G2	786 (57.6)
G3	578 (42.4)
Missing, n	51
Hormone receptor status, n (%)	
ER positive /PR positive	867 (64.1)
ER negative / PR negative	239 (17.7)
Missing (n)	63
HER2 receptor status (2002–2009)	
Known, n	660
Positive, n (%)	113 (17.1)
'Triple negativity' (2002–2009)	
ER/PR/HER2 known, n	660
Positive, n (%)	70 (10.6)
St. Gallen risk score (2002–2009)	
Known ER/PR/HER2 status[a], n	579
Low, n (%)	82 (14.2)
Intermediate, n (%)	400 (69.1)
High, n (%)	97 (16.7)

BMI = body mass index, ER = estrogen receptor, PR = progesterone receptor.
[a] Only applicable for patients who had primary surgery (i.e. pTNM classification).

Statistical Analysis

To evaluate the impact of BMI and age on tumor characteristics (tumor size and stage, histological subtype, grading, hormonal receptor status, HER2 status, 'triple-negative' status and the St. Gallen risk score) we created multivariate models (linear or logistic regression) including BMI and patient's age at diagnosis for (1) the entire cohort (n = 1,415), and (2) for postmenopausal women only (n = 1,063). Results of linear regression models are reported as beta-coefficients and corresponding 95% CIs; results of logistic regression models are reported as ORs with corresponding 95% CIs. Statistical analyses were performed with R Development Core Team software, version 2.5.0 (Vienna, Austria).

Data collection methods and study design were approved by the Institutional Ethical Review Board.

Results

Of the 1,415 BC patients included in the present study, 50.3% had normal body weight (BMI 18.5–< 25 kg/m^2), 30.0% were overweight (BMI 25–< 30 kg/m^2) and 17.0% obese (BMI ≥ 30 kg/m^2); the median age was 61 years (range: 26–95). Clinicopathological features of this cohort of patients are summarized in table 1.

Table 2 shows the associations between tumor characteristics, BMI and age. The multivariate analyses included the directly measured BMI (as a continuous variable) and patient's age, each at the time of the initial cancer diagnosis.

With regard to the impact of age on tumor characteristics, the present study revealed a positive association between advancing age and the probability of being diagnosed with lobular instead of ductal BC (OR = 1.18; 95% CI = 1.06–1.32, p = 0.003). Furthermore, increasing age was associated with a more favorable grading (OR = 0.91; 95% CI = 0.84–0.98, p = 0.019) and a higher probability of a positive ER status (OR = 1.23; 95% CI = 1.11–1.35, p < 0.001). With increasing age, TNBC were diagnosed less often (OR = 0.71; 95% CI = 0.59–0.86). No associations were observed between advancing age and tumor size (independent of detection modus), TNM and HER2 status, and St. Gallen risk score.

Table 2. Association of BMI and age with prognostic relevant breast cancer characteristics

	Entire cohort	p value[a]	Postmenopausal women	p value[a]
Beta-coefficient (95% CI)				
Tumor size (all patients)				
BMI[b]	0.03 (0.01–0.05)	**< 0.001**	0.03 (0.01–0.05)	**0.002**
Age[c]	0.01 (0–0.02)	0.082	0.01 (0.02–0.05)	**< 0.001**
Tumor size (tumor detected by self-examination)				
BMI[b]	0.05 (0.03–0.07)	**< 0.001**	0.04 (0.02–0.06)	**< 0.001**
Age[c]	0.001 (0–0.02)	0.188	0.01 (-0.01–0.03)	0.349
Tumor size (tumor detected by mammography or sonography)				
BMI[b]	0.03 (0–0.07)	**0.044**	0.03 (0.0–0.07)	0.076
Age[c]	0 (-0.03–0.03)	0.840	0.02 (-0.03–0.06)	0.457
OR (95% CI)				
TNM stage (III/IV vs. I/II)				
BMI[b]	1.16 (1.02–1.31)	**0.022**	1.06 (0.92–1.23)	0.402
Age[c]	0.97 (0.89–1.06	0.525	1.01 (0.88–1.17)	0.833
Histological subtype (lobular vs. ductal)				
BMI[b]	1.04 (0.89–1.22)	0.602	1.05 (0.89–1.25)	0.573
Age[c]	1.18 (1.06–1.32)	**0.003**	1.09 (0.92–1.28)	0.324
Grading (3 vs. 1 and 2)				
BMI[b]	1.11 (1.00–1.25)	0.057	1.10 (0.97–1.2)	0.135
Age[c]	0.91 (0.84–0.98)	**0.019**	0.91 (0.81–1.03)	0.151
ER status (positive vs. negative)				
BMI[b]	0.95 (0.83–1.09)	0.459	0.99 (0.84–1.16)	0.874
Age[c]	1.23 (1.11–1.35)	**< 0.001**	1.20 (1.02–1.40)	**0.025**
HER2 status (2002–2009: positive vs. negative)				
BMI[b]	0.92 (0.74–1.15)	0.467	0.92 (0.72–1.18)	0.526
Age[c]	0.95 (0.82–1.10)	0.495	0.97 (0.77–1.22)	0.786
'Triple negativity' (2002–2009: yes vs. no)				
BMI[b]	1.19 (0.93–1.52)	0.165	0.87 (0.64–1.17)	0.350
Age[c]	0.71 (0.59–0.86)	**< 0.001**	1.35 (0.99–1.84)	0.052
St. Gallen risk score (2002–2009: high vs. low)				
BMI[b]	1.24 (1.00–1.55)	0.049	1.20 (0.94–1.53)	0.154
Age[c]	0.88 (0.75–1.02)	0.091	0.89 (0.70–1.12)	0.308

BMI = body mass index, CI = confidence interval, OR = odds ratio, ER = estrogen receptor.

[a] p value: statistically significant: < 0.05.

[b] per 5 BMI units. [c] per 10 years.

Regarding the impact of BMI on tumor characteristics, increasing BMI was associated with increasing tumor size in the entire cohort, such that the tumor increased by 3 mm per 5 unit change in BMI (beta-coefficient 0.03; 95% CI = 0.01–0.05, $p < 0.001$) and in patients who found the tumor by self-palpation (beta-coefficient = 0.05; 95% CI = 0.03–0.07, $p < 0.001$) as well as in women in whom the cancer was detected by radiological examination (mammography or sonography) (beta-coefficient = 0.03; 95% CI = 0–0.07, $p = 0.044$).

Increasing BMI was also related to more advanced TNM stage at diagnosis (OR = 1.16; 95% CI = 1.02–1.31, $p = 0.022$), unfavorable grading (OR = 1.11; 95% CI = 1.00–1.25, $p = 0.057$) and a higher St. Gallen risk score (OR = 1.24; 95% CI = 1.00–1.55, $p = 0.049$). No significant associations were observed between BMI and histological subtype (lobular vs. ductal), positive ER status, positive HER2 status, and the presence of a TNBC.

Limiting the group of women to postmenopausal BC patients attenuated the results mentioned above, but did not change the direction of the correlations/associations (see table 2) with the exception of triple negativity and age.

Discussion

There is increasing evidence that BMI is inversely associated with BC prognosis [1, 7, 17]. However, at present, the causal mechanisms are still under investigation. This may partly be due to a poor compliance to BC screening. Compliance and persistence with medical measures are strongly determined by personal motivations, which are determined by a considerable number of individual psychosocial and medical factors. Few published studies have evaluated the impact of body weight on compliance and persistence with BC therapy [2, 24–26]. However, the complex relationship between BMI and acceptance of medical measures has been rather well examined with regards to mammography screening rates. Some authors reported significantly lower compliance with BC screening in obese women [27–29], although others did not confirm this finding in a large population-based analysis of more than 130,000 women [30]. The reasons why a significant number of obese patients delay or refuse to participate in cancer screening programs are not yet fully understood. One of the most common reasons women give is the embarrassment of being weighed or having to undergo a physical exam with even more embarrassing aspects to endure (e.g. too small gowns, examination tables, instruments) [28, 29, 31]. A further crucial point is the physician's attitude towards obese patients. The literature reports a considerable amount of negative and stereotypical attitudes toward obese patients that can be interpreted as decreased respect for obese patients [29, 32, 33]. This attitude is clearly felt by the patients, influencing them in their behavior and decisions [32–34]. Efforts are needed to avoid these deterrents.

The worse outcome in obese women could also be due to more advanced stage at diagnosis and/or the difficulty in palpating these tumors. Additionally, obese BC patients may have more aggressive cancers [17]. Obesity is accompanied with the up-regulation of various cellular proliferation pathways [35]. Adipokines and estrogens, produced in adipose tissue, may enhance tumor cell proliferation and metastasis [35–37], and may potentially result in more aggressive ER-positive cancers in postmenopausal women [16].

In the present study, BMI was significantly associated with tumor size. This applied not only to the cases in which the tumor was found by self-detection, but also to lesions detected by radiological breast examinations. In addition, a higher BMI was positively correlated with advanced TNM stage, unfavorable grading, and a higher St. Gallen risk score. No associations were observed between BMI and histological subtype, ER status, HER2 status and TNBC. Higher age, on the other hand, increased the probability of lobular instead of ductal BC, less TNBC, ER positivity and more favorable grading. In the subgroup of postmenopausal women, the above-mentioned findings were attenuated but did not change the direction of the associations.

Age and Prognostically Relevant Tumor Characteristics

BC in elderly women seems to be of a less aggressive nature than in younger patients [38]. Our observed associations with age are in accordance with the findings in the literature for Caucasian women [39]. At a higher age, tumors are more often ER positive [39–42]. In the study by Parise et al. [39], the increase in the percentage of the $ER^+/PR^+/HER2^-$ subtype with increasing age almost mirrored the increasing proportion of BC cases in white women [39]. This BC subtype has the best overall 5-year relative cumulative survival [40]. On the other hand, the triple negative subtypes are found more often in younger than in older women [39, 40, 43–45].

BMI and Breast Cancer: Tumor Size, TNM stage, Grading, and St. Gallen Risk Score

Although in several reports obesity was positively associated with advanced stage, increased tumor size and unfavorable grading of breast carcinomas at diagnosis, these findings were not confirmed in other surveys [7]. Accordingly, Wasserman et al. [46] observed no association between BMI and disease stage at diagnosis in 301 postmenopausal women of the Women's Healthy Eating and Living study. The same was true for women of any age in another study [47]. Similarly, in the study by Chagpar et al. [7], no association was observed between BMI and tumor size, lymph node status, or disease stage at diagnosis in mostly postmenopausal women with hormonally sensitive BC. In contrast, several other studies observed a positive association between BMI and disease stage, tumor size and lymph node status at diagnosis [5, 6, 48], as we did in our survey for tumor size and stage. In a study carried out in the canton of Geneva, Switzerland [2], invasive

carcinomas larger than 1 cm were more frequently impalpable in obese women (22%) than in normal/underweight women (12%). It may be more difficult for clinicians and women to palpate a tumor in a large breast than in a small one. Thus, obese women with larger breasts may have larger tumors and more advanced tumor stages at diagnosis than lean women with small breasts. Accordingly, in a study of 2,863 patients diagnosed with BC in Wisconsin, elevated BMI was associated with a greater probability of nonlocalized tumors in self-detected cancers, but in women whose tumors were found by screening mammography or by clinical breast examination, BMI was not related to disease stage [49]. In the present study, however, BMI was found to be a significant factor for tumors found by self-detection, as well as for those detected by radiological breast examinations. Thus, either both methods for tumor detection are impaired by large breasts, or larger tumors in larger breasts could be the consequence of obesity. In this context, the results of an Australian study [50] on the outcome of mammography in women with large breasts is of interest: the sensitivity and specificity of mammography were greater in women with larger breasts than in other women.

Non-adherence to BC screening is another possible explanation for our findings. Obese women are less likely to follow physician's recommendations for breast and cervical cancer screening [29]. On the basis of 10 studies, among women in the U.S., Cohen et al. found that obesity most likely is a barrier to screening for BC, particularly among white women [51], although this is not universally so [52]. In the present study, we could not comment on this explanation because until now only opportunistic screening exists in the Basel region.

BMI and Breast Cancer: ER status, HER2 status and TNBC

Obesity may affect BC risk by increasing circulating endogenous estrogen levels [53]. Thus, the association between body weight and BC risk may be modified by the tumor's ER and PR status. The summarized findings of 9 cohort and 22 case-control studies comparing the highest versus the reference categories of relative body weight observed that the risk for ER^+PR^+ tumors was 20% lower (95% CI = -30 to -8%) among premenopausal and 82% higher (95% CI = 55–114%) among postmenopausal women [15]. No associations were observed for ER^-PR^- or ER^+PR^- tumors. More recent studies confirmed these findings [2, 12, 54, 55]. The association between BMI and BC risk is thus dependent on the tumor's ER/PR status and the woman's menopausal status, and in some studies the risk was modified by hormone replacement therapy (HRT) [42, 55, 56].

In addition, HER2 status may be inversely associated with BMI, independent of ER status [57], as shown in a study of postmenopausal women. Phipps et al. [58], on the other hand, found no difference in the association between BMI and HER2 status. Additional studies with sufficient numbers of HER2-positive and HER2-negative tumors are needed to clarify the association between HER2 status and BMI.

Data examining obesity as a risk factor for TNBC are limited and inconsistent [59, 60]. Case-control studies that evaluated BMI in women irrespective of menopausal status and in postmenopausal women found no association with TNBC [58, 60–62]. Pooling 2 case-control studies revealed a positive association between BMI and TNBC (OR = 2.7; 95% CI = 1.0–7.5) in postmenopausal women not using HRT [58]. No association was observed in HRT users. In a prospective study, for postmenopausal women in the highest versus the lowest BMI quartile, Phipps et al. [12] observed a 1.35-fold (95% CI = 0.92–1.99) non-significantly increased risk of TNBC without association with HRT use.

Strength and Limitations

One of the strengths of our study is the comprehensive data set prospectively collected from a university breast center covering a recent study period (1997–2009). Furthermore, for our predictor variable 'BMI' we only used directly measured BMI data. These are much more reliable than self-reported BMI data [63]. Individuals tend to underestimate their weight and overestimate their height. BMI was relatively stable over the entire study period. It is a distinct finding in the Swiss general population that overweight and obesity rates have remained comparatively stable over the last 12 years [18]. Furthermore, we demonstrated that this BMI trend in the general population was similar to that in a cohort of BC patients [64].

However, the limitations of our study must also be considered. The numbers of triple-negative and HER2-positive cases were small, reflecting the rarity of these tumor types, and this limits the possibilities of drawing meaningful conclusions about the association of BC with BMI for these cases. Moreover, HRT use and screening for BC could not be taken into account in the present analysis due to lack of adequate data in these areas.

Conclusion

In the present study, BMI was a significant factor for tumor size at diagnosis; this applied not only to the cases in which the tumor was found by self-detection, but also to lesions detected by radiological breast examinations. Even though these results strengthen the evidence for a causal relationship between BMI and BC outcome, we cannot exclude non-adherence to screening for BC as a possible explanation for our findings.

Disclosure Statement

The authors declare that there are no financial or personal relationships with other people or organizations that could inappropriately influence the work reported or the conclusions, implications, or opinions stated.

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