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EPIDEMIOLOGY

Impact of obesity on diagnosis and treatment of breast cancer

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Abstract In this population-based study, we evaluated the impact of obesity on presentation, diagnosis and treatment of breast cancer. Among all women diagnosed with invasive breast cancer in the canton Geneva (Switzerland) between 2003 and 2005, we identified those with information on body mass index (BMI) and categorized them into normal/underweight (BMI <25 kg/m^2), overweight (BMI ≥–<30 kg/m^2) and obese (BMI ≥30 kg/m^2) women. Using multivariate logistic regression, we compared tumour, diagnosis and treatment characteristics between groups. Obese women presented significantly more often with stage III–IV disease (adjusted odds ratio [OR$_{adj}$]: 1.8, 95% CI: 1.0–3.3). Tumours ≥1 cm and pN2-N3 lymph nodes were significantly more often impalpable in obese than in normal/underweight patients (OR$_{adj}$ 2.4, [1.1–5.3] and OR$_{adj}$ 5.1, [1.0–25.4], respectively). Obese women were less likely to have undergone ultrasound (OR$_{adj}$ 0.5, [0.3–0.9]) and MRI (OR$_{adj}$ 0.3, [0.1–0.6]) and were at increased risk of prolonged hospital stay (OR$_{adj}$ 4.7, [2.0–10.9]). This study finds important diagnostic and therapeutic differences between obese and lean women, which may impair survival of obese women with breast cancer. Specific strategies are needed to optimize the care of obese women with or at risk of breast cancer.

Keywords Obesity · Breast cancer · Diagnosis · Treatment · Population-based

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Introduction

The relationship between obesity and breast cancer is complex. Most epidemiological studies show that various measures of obesity are associated with a significant increase in the risk of post-menopausal breast cancer [1, 2], while an inverse relationship exists for pre-menopausal women [3].

There is accumulating evidence that obesity is associated with adverse overall and disease-free survival for both pre- and post-menopausal breast cancers [1, 4–6]. More advanced stage at diagnosis [7], unfavourable tumour characteristics [8] and suboptimal local and systemic treatment [9] have been suggested to contribute to this detrimental prognosis.

Because of the increasing prevalence of obesity, in combination with the high rates of breast cancer worldwide, it is crucial to better understand the mechanisms behind the impaired outcome of breast cancer associated with obesity. In this population-based study, we assessed the impact of obesity on presentation, diagnosis and treatment of breast cancer in routine health care setting.

Materials and methods

We used data of the Geneva Cancer Registry, which records all incident cancers occurring in the population of the canton Geneva in Switzerland. Information is considered accurate, as attested by the low percentage (<2%) of cases registered by death certificate only [10]. Trained registrars systematically collect information from various sources and abstract data from medical files of all hospitals, private practitioners and pathology laboratories in the canton. Physicians regularly receive questionnaires to complete missing data. Recorded data include sociodemographic variables, tumour characteristics, stage at diagnosis and treatment received within the first 6 months after diagnosis. Since 2003, additional information, including body measurements, was collected in the context of a larger research of the Swiss Association of Cancer Registries, investigating the pattern for breast cancer care in Switzerland.

For the purpose of our study, we identified all women resident in the canton of Geneva (Switzerland) diagnosed with histologically confirmed invasive breast cancer between 1 January 2003 and 31 December 2005 ($n = 1{,}110$). We excluded women with breast cancer detected at autopsy ($n = 5$). Weight and height were retrieved from the medical files and available for 460 out of 1,110 cases (41%).

These 460 individuals study cohort is representative of the population-based sample in terms of patient and tumour characteristics, except for the type of health insurance; since height and weight were more often recorded or retrieved in the file of patients treated in the public hospital, 72% of the women had basic health insurance in the study cohort compared with 52% in the population-based one.

We recorded weight measured within 6 months after diagnosis. The body mass index (BMI) was calculated as the weight divided by the square metre of the height and was further categorized according to the WHO criteria: normal/underweight (BMI <25 kg/m^2), overweight (BMI ≥25–<30 kg/m^2) and obese (BMI ≥30 kg/m^2) [11].

Patient and tumour characteristics

Socioeconomic status was based on woman's most recent occupation or, when missing, that of the spouse and was categorized as high (executives and administrators), middle (non-manual employees), low (manual employees, skilled and unskilled workers) and unknown. Health insurance coverage was classified as basic versus private and marital status as married versus unmarried. Familial risk was categorized as high (at least one-first-degree relative with breast or ovarian cancer diagnosed before the age of 50 years), low (no affected first- or second-degree relatives with breast or ovarian cancer), moderate (all other known family histories) and unknown.

For staging, we used the pathological tumour node metastasis (pTNM) classification system, or, when not available, the clinical tumour node metastasis (cTNM) classification. [12] Stage was classified as stage I (T0/T1 and N0), stage II (T0/T1 and N1, or T2 and N0/N1, or T3/N0), stage III (T0/T1/T2 and N2, or T3 and N1/N2, or T4 and any N, or any T and N3), stage IV (any T, any N, M1), unknown and further categorized as stage I/II versus III/IV. We also recorded pathological tumour size (in millimetres) and palpability of tumour and axillary lymph nodes (palpable [cT1-4 or cN1-4] versus non-palpable [cT0 or cN0]).

Histological subtype was categorized as ductal (ICD-O 8500), lobular (ICD-O 8520 and 8522) and other [13]. Tumour differentiation was classified as good, moderate, poor and unknown. Presence of an in situ component was recorded and classified as present or absent, lymphovascular invasion and multicentricity as yes versus no.

Oestrogen receptor [ER] and progesterone receptor [PR] status were determined by standard immunohistochemical reaction. Tumours expressing hormone receptors in <10% of the cells were considered receptor negative and those expressing receptors in ≥10% as receptor positive. ER and PR status was regrouped as ER+/PR+, ER+/PR−, ER−/PR+, ER−/PR− and unknown. HER-2 expression was recorded as amplified or not, based on immunohistochemistry or on the HER-2 gene amplification test by fluorescence in situ hybridization.

Diagnostic and treatment characteristics

We categorized method of tumour detection into screening (opportunistic or organized screening mammography, ultrasound or clinical periodic breast examination), breast self-examination, tumour symptoms (nipple discharge, peau d'orange) and fortuitous discovery (during workup of another unrelated illness). Use of mammography, ultrasound and magnetic resonance imaging (MRI) was coded as performed versus not performed.

For loco-regional treatment, we classified surgery as breast-conserving surgery, mastectomy and not performed. Margins for invasive and in situ components were extracted from pathology reports (positive margins, margins of <1 mm, 1–10 mm, >10 mm). Sentinel lymph node biopsy and axillary dissection were classified as performed versus

not performed. Radiotherapy was coded as yes versus no. With the collected dates of hospitalisation, we computed the number of days spent in hospital for the first surgical intervention and categorized it in <5 days, 6–10 days and >10 days.

Systemic therapies (hormone therapy, chemotherapy and trastuzumab) were categorized as administered versus not administered.

Statistics

Chi-square test was used to compare patient, tumour, diagnosis and treatment characteristics between normal/underweight (BMI <25 kg/m^2), overweight (BMI ≥25 and <30 kg/m^2) and obese women (BMI ≥30 kg/m^2).

In order to maximize the effect of obesity, we compared obese women (BMI ≥30, $n = 86$) with normal/underweight women (BMI <25, $n = 252$), and a total of overweight women ($n = 123$, 26.7%) were excluded from further analysis.

With univariate logistic regression analysis, we identified which covariates were significantly correlated with obesity. Then, we performed different multivariate logistic regression analyses, each model having its specific variables of adjustment. Models were fitted using maximum likelihood method [14]. To identify tumour characteristics significantly and independently associated with obesity, we adjusted for age and health insurance status. Since socioeconomic status was strongly correlated to the type of health insurance, we did not include it in adjusted analysis in order to avoid colinearity. To assess the impact of obesity on diagnosis and treatment of breast cancer, we adjusted for demographic, tumour, diagnosis and treatment covariates associated with obesity.

We performed stratified analysis addressing tumour and lymph node palpability according, respectively, to histological tumour size and lymph node involvement, ER and PR status according to menopausal status and stage according to method of detection.

Two-tailed tests were used and statistical significance was defined at $P < 0.05$. Statistical analysis was performed with SPSS software 15.0 version (SPSS, Inc., Chicago, IL).

Results

Patient and tumour characteristics

Among the 460 women included in the study, 252 (55%) were considered as normal/underweight, 122 (26%) as overweight and 86 (19%) as obese. Obese women were significantly more often of low socioeconomic status and had more often only basic health insurance compared with normal/underweight women (Table 1). Obese (21%) and overweight (24%) women tended to be less often in the pre-menopause than normal/underweight women (31%). Presence of a positive family history was not different across BMI categories, neither were nationality, country of birth and civil status (results not shown).

Table 1 Patient characteristics and associated *P* value chi-square test according to the BMI

	BMI			*P* chi-square
	<25 $N = 252$ (%)	25 to <30 $N = 122$ (%)	≥30 $N = 86$ (%)	
Age (years)				
>70	59 (23)	36 (29)	25 (29)	0.264
50–70	116 (46)	57 (47)	44 (51)	
<50	77 (31)	29 (24)	17 (20)	
Socioeconomic status				
Middle	131 (52)	52 (43)	36 (42)	0.000
High	44 (18)	12 (10)	4 (5)	
Low	43 (17)	38 (31)	23 (27)	
Unknown	34 (13)	20 (16)	23 (26)	
Health insurance				
Basic	170 (68)	95 (78)	70 (81)	0.015
Private	82 (32)	27 (22)	16 (19)	
Menopausal status				
Post-menopause	171 (68)	93 (76)	68 (79)	0.090
Pre-menopause	79 (31)	29 (24)	18 (21)	
Unknown	2 (1)	0 (0)	0 (0)	
Family history				
High	16 (6)	11 (9)	5 (6)	0.902
Middle	65 (26)	30 (25)	23 (27)	
Low	158 (63)	79 (65)	53 (62)	
Unknown	13 (5)	2 (1)	5 (5)	

BMI body mass index

Obese women were nearly twice as likely to present with advanced stage (stage III/IV) at diagnosis compared with normal/underweight women (adjusted OR [OR_{adj}]: 1.8, 95% CI: 1.0–3.3) (Table 2). Among women who detected their tumour by means of self-examination, 40% of obese against 20% of normal/underweight women had stage III/IV disease (OR_{adj}: 2.4, 95% CI: 1.0–5.9). Among women with screen-detected tumours, 6% of obese and 4% of lean women presented with stage III/IV disease (OR_{adj}: 2.1, 95% CI: 0.3–13.7).

There was no significant difference in histological type, differentiation, multicentricity, lymphovascular invasion and presence of in situ component between obese and normal/underweight women (Table 3). Obese women tended to have more often ER+/PR+ and less often ER+/PR−

Table 2 Relationship between BMI and stage at diagnosis, associated *P* value chi-square test and odds ratio of obese vs. normal/underweight women

	BMI			*P* chi-square	OR multi-adjusted for obese vs. normal/underweight (95% CI)[a]	
	<25 $N = 252$ (%)	25 to <30 $N = 122$ (%)	≥30 $N = 86$ (%)			
Stage at diagnosis						
I	111 (44)	47 (38)	29 (34)	0.288	1	Ref.
II	98 (39)	54 (44)	31 (36)		0.9	(0.5–1.8)
III	28 (11)	13 (11)	16 (19)		2.1	(0.9–5.2)
IV	11 (4)	7 (6)	8 (9)		2.5	(0.8–7.3)
Unknown	4 (2)	1 (1)	2 (2)	–	–	
Stage in two categories						
I/II	209 (83)	101 (83)	60 (70)	0.026	1	Ref.
III/IV	39 (15)	20 (16)	24 (28)		1.8	(1.0–3.3)*
Unknown	4 (2)	1 (1)	2 (2)	–	–	
For cancer detected by self-examination						
I/II	78 (80)	32 (82)	21 (58)	0.024	1	Ref.
III/IV	19 (19)	6 (16)	14 (39)		2.4	(1.0–5.9)°
Unknown	1 (1)	1 (2)	1 (3)	–	–	
For cancer detected by screening						
I/II	101 (96)	54 (93)	30 (91)	0.660	1	Ref.
III/IV	4 (4)	4 (7)	2 (6)		2.1	(0.3–13.7)
Unknown	0 (0)	0 (0)	1 (3)	–	–	

BMI body mass index; *CI* confidence interval; *OR* odds ratio; *Ref* reference

* $P < 0.05$; ° $0.07 < P > 0.05$

[a] OR adjusted for age and health insurance type

tumours when compared with normal/underweight women (OR_{adj}: 0.4, 95% CI: 0.2–1.0). No significant difference was found for ER and HER-2 status (results not shown).

Diagnosis and treatment characteristics

There was no significant difference in method of tumour detection between obese and non-obese women (Table 4). Diagnostic workup of obese women included significantly less often ultrasound (OR_{adj}: 0.5, 95% CI: 0.3–0.9) or MRI (OR_{adj}: 0.3, 95% CI: 0.1–0.6).

Overall, palpability of the primary tumour and of axillary lymph nodes was comparable between the three groups. However, after stratification by tumour size, tumours larger than 1 cm were more frequently impalpable in obese women (22%) than in normal/underweight women (12%) (OR_{adj}: 2.4, 95% CI: 1.1–5.3). Similarly, in obese women with extensive axillary involvement (pN2-3), axillary nodes were more often impalpable than in normal/underweight women (54 vs. 19%, respectively; OR_{adj}: 5.1, 95% CI: 1.0–25.4).

Compared with normal/underweight women, obese women underwent significantly less often mastectomy (OR_{adj}: 0.3, 95% CI: 0.2–0.7) (Table 5). In addition, they had less often narrow margins (<10 mm) after their first surgical intervention, both for invasive (OR_{adj}: 0.3, 95% CI: 0.1–0.5) and in situ components (OR_{adj}: 0.2, 95% CI: 0.1–0.5). There was no significant difference in use of sentinel lymph node biopsy, axillary dissection or administration of radiotherapy after breast-conserving surgery.

Obese and overweight women had a higher risk of prolonged hospital stay after surgery: 67% of obese and 66% of overweight women were hospitalized for more than 5 days compared with 46% of normal/underweight women ($P = 0.019$). After correction for health insurance type, age, stage and type of surgery, the risk of prolonged hospital stay remained significantly increased for obese women versus normal/underweight women: OR_{adj} of 4.5 (95% CI: 1.9–10.8) for a stay of more than 5 days and OR_{adj} of 13.3 (95% CI: 2.3–78.0) for a stay of more than 10 days.

Hormone therapy, chemotherapy and trastuzumab were equally prescribed between the two groups (results not shown).

Discussion

This population-based study shows that obesity affects presentation, diagnostic assessment and management of obese women with breast cancer. Notably, they present with more advanced stage at diagnosis and encounter more difficulties in clinical detection of primary tumours and enlarged axillary lymph nodes. In addition, diagnostic workup of obese and overweight women includes less often ultrasound and MRI. Finally, obese women are at increased risk of prolonged hospital stay.

Table 3 Tumour characteristics, associated *P* value chi-square test according to BMI and odds ratio of obese vs. normal/underweight women

	BMI			*P* chi-square	OR multi-adjusted for obese vs. normal/underweight (95% CI)[a]	
	<25 *N* = 252 (%)	25 to <30 *N* = 122 (%)	≥30 *N* = 86 (%)			
Differentiation						
Good	60 (24)	33 (27)	21 (25)	0.344	1	Ref.
Moderate	148 (59)	57 (47)	51 (59)		0.9	(0.5–1.8)
Poor	37 (14)	28 (23)	12 (14)		1.1	(0.5–2.5)
Unknown	7 (3)	4 (3)	2 (2)	–	–	
Multicentricity						
No	162 (64)	73 (60)	57 (66)	0.738	1	Ref.
Yes	66 (26)	37 (30)	19 (22)		1.2	(0.7–2.1)
Unknown	24 (10)	12 (10)	10 (12)	–	–	
Lymphatic invasion						
No	157 (62)	80 (66)	54 (63)	0.484	1	Ref.
Yes	25 (10)	17 (14)	8 (9)		1.0	(0.4–2.6)
Unknown	56 (28)	25 (20)	24 (28)	–	–	
In situ component						
No	66 (26)	32 (61)	27 (32)	0.080	1	Ref.
Yes	153 (61)	74 (26)	39 (45)		0.7	(0.4–1.3)
Unknown	33 (13)	16 (13)	20 (23)	–	–	
Receptor status						
ER/PR						
ER+/PR+	170 (67)	84 (69)	66 (77)	0.213	1	Ref.
ER+/PR−	41 (16)	16 (13)	7 (8)		0.4	(0.2–1.0)°
ER−/PR−	37 (15)	21 (17)	12 (14)		0.9	(0.4–1.8)
ER−/PR+	2 (1)	1 (1)	0 (0)		NA	
Unknown	2 (1)	0 (0)	1 (1)	–	–	
PR in post-menopausal patients						
<10%	52 (30)	24 (26)	13 (19)	0.083	1	Ref.
10–50%	43 (25)	28 (30)	14 (21)		1.3	(0.6–3.1)
>50%	75 (44)	40 (43)	40 (59)		2.1	(1.0–4.4)*
Unknown	1 (1)	1 (1)	1 (1)	–	–	
ER in post-menopausal patients						
<10%	23 (13)	11 (12)	7 (10)	0.874	1	Ref.
10–50%	12 (7)	7 (7)	3 (4)		0.9	(0.2–4.3)
>50%	135 (79)	74 (80)	57 (84)		1.5	(0.6–3.7)
Unknown	1 (1)	1 (1)	1 (2)	–	–	

BMI body mass index; *CI* confidence interval; *ER* oestrogen receptors; *Her-2* human epidermal growth factor receptor 2; *NA* not applicable; *OR* odds ratio; *PR* progesterone receptors; *Ref* reference

* $P < 0.05$; ° $0.07 < P > 0.05$

[a] OR adjusted for age and health insurance type

The presence of a positive association between advanced stage at diagnosis and obesity is corroborated by several studies [5, 15–19].

One explanation could be that various biological factors related to obesity stimulate tumour progression. The high concentration of bioavailable oestrogen due to aromatization of circulating androgens to oestrogen in adipose tissues may have a mitogenic effect on breast cancer cells of obese women with hormone-dependent tumours [20]. Some studies have reported that obesity has a stronger negative impact on breast cancer prognosis in patients with hormone receptor positive tumours [21, 22]. In accordance with several prospective [23–25] and case–control studies [26, 27], we found that obese women tended to have more often ER+/PR+ and less often ER+/PR− tumours compared with normal/underweight women. Higher PR expression in obese women was reported previously [25, 28, 29], and could be an effect of the ER processing stimulation by higher concentration of bioactive oestrogen [30].

Other hormonal and biological processes associated with obesity, such as insulin-like growth factors, cytokines and leptin could also be related to tumour cell proliferation in obese women [31, 32]. A recent study among patients with resected colorectal cancer showed that higher levels of

Table 4 Diagnostic characteristics, associated *P* value chi-square test according to BMI and odds ratio of obese vs. normal/underweight women

	BMI			*P* chi-square	OR multi-adjusted for obese vs. normal/underweight (95% CI)	
	<25 *N* = 252 (%)	25 to <30 *N* = 122 (%)	≥30 *N* = 86 (%)			
Method of detection						
Self-examination	98 (39)	39 (32)	36 (42)	0.878	1	Ref.
Screening	105 (41)	58 (47)	33 (38)		1.0[b]	(0.5–1.8)
Symptoms	37 (15)	18 (15)	14 (16)		0.9[b]	(0.4–1.9)
Fortuitous	10 (4)	6 (5)	3 (4)		0.9[b]	(0.2–3.7)
Unknown	2 (1)	1 (1)	0 (0)	–	–	
Radiological examination						
Mammography				0.684		
Not performed	23 (9)	8 (6)	10 (12)		1	Ref.
Performed	227 (90)	113 (93)	76 (88)		0.7[b]	(0.3–1.5)
Unknown	2 (1)	1 (1)	0 (0)	–	–	
Ultrasound						
Not performed	46 (18)	20 (16)	26 (30)	0.029	1	Ref.
Performed	206 (82)	102 (84)	60 (70)		0.5[b]	(0.3–0.9)*
MRI						
Not performed	168 (66)	94 (77)	77 (90)	0.001	1	Ref.
Performed	83 (33)	28 (23)	9 (10)		0.3[b]	(0.1–0.6)**
Unknown	1 (1)	0 (0)	0 (0)	–	–	
Clinical examination						
Palpability of primary tumour						
Palpable	191 (76)	96 (79)	62 (72)	0.762	1	Ref.
Impalpable	41 (16)	19 (16)	18 (21)		1.2[a]	(0.6–2.1)
Unknown	20 (8)	7 (5)	6 (7)	–	–	
Palpability of primary tumour according to its size						
<1 cm						
Palpable	28 (53)	11 (61)	4 (45)	0.426	1	Ref.
Impalpable	20 (38)	7 (39)	3 (33)		1.3[a]	(0.2–7.4)
Unknown	6 (9)	0 (0)	2 (22)	–	–	
≥1 cm						
Palpable	134 (80)	69 (80)	45 (73)	0.254	1	Ref.
Impalpable	19 (12)	11 (13)	14 (22)		2.4[a]	(1.1–5.3)*
Unknown	14 (8)	6 (7)	4 (5)	–	–	
Palpability of lymph nodes (LN)						
Palpable	59 (23)	34 (28)	18 (21)	0.146	1	Ref.
Impalpable	187 (74)	*86* (70)	62 (72)		1.2[a]	(0.6–2.1)
Unknown	6 (3)	*2* (2)	6 (7)	–	–	
Palpability of LN according to LN involvement						
pN1						
Palpable	19 (32)	9 (27)	7 (39)	0.152	1	Ref.
Impalpable	38 (65)	23 (70)	8 (44)		0.5[a]	(0.2–1.7)
Unknown	2 (3)	1 (3)	3 (17)	–	–	
pN2-N3						
Palpable	17 (81)	6 (75)	5 (46)	0.108	1	Ref.
Impalpable	4 (19)	2 (25)	6 (54)		5.1[a]	(1.0–25.4)*
Unknown	0 (0)	0 (0)	0 (0)	–	–	

BCS breast-conserving surgery; *BMI* body mass index; *CI* confidence interval; *LN* lymph node; *MRI* magnetic resonance imaging; *OR* odds ratio; *Ref* reference

* $P < 0.05$, ** $P < 0.01$

[a] OR adjusted for age and health insurance type

[b] OR adjusted for age, health insurance type and stage

Table 5 Loco-regional treatment characteristics, associated *P* value chi-square test according to BMI and odds ratio of obese vs. normal/ underweight women

	BMI			*P* chi-square	OR multi-adjusted for obese vs. normal/ underweight (95% CI)	
	<25 *N* = 252 (%)	25 to <30 *N* = 122 (%)	≥30 *N* = 86 (%)			
Surgery						
BCS	166 (66)	89 (73)	63 (73)	0.046	1	Ref.
Mastectomy	69 (27)	25 (20)	12 (14)		0.3[a]	(0.2–0.7)**
No surgery	17 (7)	8 (7)	11 (13)	–	–	
Margin status						
For invasive component						
≥10 mm	36 (15)	17 (15)	22 (29)	0.008	1	Ref.
<10 mm	187 (81)	86 (75)	47 (63)		0.3[b]	(0.1–0.5)***
Unknown	9 (4)	11 (10)	6 (8)	–	–	
For in situ component						
≥10 mm	20 (12)	10 (12)	12 (28)	0.009	1	Ref.
<10 mm	144 (83)	65 (78)	25 (58)		0.2[b]	(0.1–0.5)***
Unknown	9 (5)	8 (10)	6 (14)	–	–	
Length of hospital stay						
<5 days	64 (54)	21 (34)	15 (33)	0.019	1	Ref.
6–10 days	50 (43)	37 (60)	26 (56)		4.5[b]	(1.9–10.8)**
>10 days	4 (3)	4 (6)	5 (11)		13.3[b]	(2.3–78.0)**
Radiotherapy						
Performed	177 (70)	95 (78)	67 (78)	0.349	1	Ref.
Not performed	71 (28)	26 (21)	19 (22)		0.8[b]	(0.3–2.4)
Unknown	4 (2)	1 (1)	0 (0)	–	–	

BCS breast-conserving surgery; *BMI* body mass index; *CI* confidence interval; *OR* odds ratio; *Ref* reference

* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$

[a] OR adjusted for age, health insurance type and stage

[b] OR adjusted for age, health insurance type, stage and type of surgery

insulin and lower levels insulin-like growth factor binding protein were associated with increased mortality, indicating that these factors could be potential mediators of an association between life style factors and mortality after colorectal cancer [33]. Obesity is often a marker for unhealthy lifestyle habits, including excess saturated fat intake and decreased level of physical activity, which are increasingly being recognized as risk factors for adverse prognosis of cancer [34].

Other mechanisms besides more aggressive tumour behaviour may account for advanced stage and impaired prognosis of obese women with breast cancer, in particular differences in diagnosis and treatment.

We found the relationship between BMI and stage to be associated with the method of cancer detection, obese women having more often advanced stage when the tumour was detected by self-examination. Similarly, in some research [35], but not all [36], the association between increased BMI and advanced stage was restricted to women who self-detected their cancer, thus suggesting that advanced stage may be due to delayed diagnosis because of difficulties in detecting breast lumps in obese women. This concept is supported by studies showing a positive association between breast size and stage of breast cancer [35–37]. Likewise, we found that obese women with large tumours or extensive lymph node involvement were significantly more likely to have impalpable primary tumours or axillary lymph nodes, which could lead to delay in seeking medical attention.

Advanced stage at diagnosis could also be a consequence of delayed medical consultation by obese women because of embarrassment regarding their weight and appearance [38–41]. Obese women have been shown to be twice as likely to postpone doctor's visit for more than 3 months after occurrence of first symptoms, resulting in advanced stage of disease at presentation [42].

Another explanation for advanced stage at diagnosis could be difference in radiological workup. Even though similar proportions of obese and non-obese women were detected by screening mammography in our study, obese women underwent less often ultrasound and MRI as part of their diagnostic workup. They may encounter negative attitudes from health professionals, thus increasing the risk of low compliance to radiological examination [38, 43]. Also, the lack of adapted radiological equipment (i.e. MRI) for severely obese women could interfere with their diagnosis process.

This study also shows that obesity has a dual impact on loco-regional treatment of breast cancer. On one hand, obese women underwent less frequently mastectomy and had more frequently large tumour-free margins, suggesting it may be easier to achieve better oncological results and

aesthetic outcome in surgery of larger breast. On the other hand, obesity seems to have an unfavourable effect on the recovery after breast cancer surgery, as obese women had more often prolonged hospital stay. High BMI has been identified as a significant and independent risk factor for complications after breast or axillary surgery, such as wound infections or lymphoedema [44–47]. In addition, obese women may need more time to recover after surgery due to complications linked to the higher prevalence of comorbid conditions, which may impact on breast cancer outcome by consequently postponing subsequent radiotherapy and adjuvant treatments.

In accordance with another study [48], we did not find any difference in access to radiotherapy following breast-conserving surgery and the use of systemic treatment between BMI categories. Nevertheless, we had no insight into the quality and effectiveness of systemic treatments, whereas obesity is increasingly reported to be associated with a reduced dose for the first cycle of chemotherapy [49, 50], suggesting that physicians may use the ideal body weight for the dose calculation to avoid overdosing and toxicity. Recently, Litton et al. [5] showed that the relationship between higher BMI and a worse pathological response rate after neoadjuvant chemotherapy was associated with worse overall survival.

We acknowledge that our study suffers from some limitations. First of all, information on BMI was only available for 41% of the population-based cohort. As height and weight were better recorded at the public hospitals, our study sample shows an over-representation of women with basic health insurance. However, we believe that, by adjusting for health insurance type, the association between obesity and tumour diagnosis and treatment characteristics is valid. Nevertheless, our study may have overestimated the prevalence of obesity in Geneva breast cancer patients, as women with basic health insurance had a higher tendency towards obesity.

Also, by using a single measure of body weight, we did not take weight changes during diagnosis and treatment process into account. Even though the baseline body weight would be more relevant when evaluating diagnosis aspects of the disease, it may be less so when analyzing the pattern of care.

Finally, the small sample size prevents us for drawing definite conclusion, and the results should be used to generate hypothesis as well as need confirmation in larger data sets.

In conclusion, our results emphasize that obesity has an impact on diagnosis and treatment of breast cancer, which may partly explain the impaired outcome associated with obesity. These results indicate the need for more tailored care of obese patients with breast cancer. Women and clinicians have to be informed on the limited value of breast (self-) examination associated with obesity. Also, specific strategies should focus on improving access to complete clinical and radiological workup, as well as on solving medical and technical constraints for the treatment of obese women with breast cancer.

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