Obesity as Prognostic Factor for Survival after Breast Cancer: Results from a population-based study.

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Background and Objectives

Obesity at diagnosis is associated with inferior survival after breast cancer in clinical or population-based studies (Ref.1). Because adjustment for potential confounding was not consistent across studies, the influence of different patient-, tumor- and treatment characteristics is still unclear. A better understanding of the relation between these factors may have important implications for the future management of the disease.
Our goal was to reassess the prognostic value of obesity at diagnosis on survival in women with breast cancer of defined histology while accounting for a range of other recognized prognostic factors.

Data and Methods

A random sample of 1012 women with primary invasive breast cancer was drawn from the Swiss cancer registries of Basel and Zürich. Diagnosis dates were between 1.1.03 and 31.12.05. Cases discovered at autopsy, first diagnosed with another tumour, local recurrence of previous breast cancer or known on the basis of death certificates only were excluded. Active follow-up ended 31.12.2008.

Body Mass Index (BMI) was used as a proxy for adiposity-level. Age was taken as proxy for the menopausal status. Oestrogene- or progesterone-positivity was defined by standard immunhistochemistry. Herceptin2 expression status (HER-2) was categorized as positive based on either immunhistochemistry or on the HER-2 gene amplification test by fluorescence in-situ hybridization.

Chi-square tests and unadjusted odds ratios were used to assess the univariate association of patient, tumour and treatment characteristics with obese (BMI≥30) and reference patients (BMI<30).

Observed (OS) and relative survival (RS) probabilities were derived based on the cohort approach. RS was calculated as the ratio of the observed probability of survival of cancer cases and the expected survival of persons in the general population of corresponding age, sex and calendar year of death.

Proportional hazard Poisson regression was performed to estimate hazard ratios and 95% confidence intervals for obesity after adjustment for patient, tumour and treatment characteristics. The prognostic significance of obesity was also assessed within subgroups defined by the other relevant breast cancer prognostic factors (menopausal status, tumour stage, oestrogen receptor status, progesterone receptor status).

Imputation procedure:
The 'Multiple Imputation by Chained Equations' algorithm as implemented in Stata™ (v12.1) was used. Univariate regression equations included all complete variables, incomplete variables with significant Spearman rank correlation (P<0.05), variables associated with missingness in the imputed variable and interaction terms for obesity indicator and stratification factors. It also included outcome variables (death indicator and survival time). Ten imputed datasets were generated for final effect estimation.

Dataset: list of variables

Variables abstracted from pathology and medical records (within 6 months after diagnosis)	Categories	% missing information
Patient characteristics		
Body mass index	Not obese (<30) / Obese (≥30)	18.9
Age at diagnosis	<55 yrs / 55-65 / 65-75 /≥75	0
Period of diagnosis (6 months)	1 / 2 / 3 / 4 / 5 / 6	0
Menopausal status	Pre (<52 yrs) / Post (≥52 yrs)	0
Family risk	Low / Moderate / High	11.1
Health insurance type	Basic / Private	12.0
Cancer registry	Basel / Zürich	0
Tumour characteristics		
Histological subtype	Ductal (ICD-O code 8500) / Lobular (ICD-O codes 8520 and 8522) / Other	0.6
Oestrogen receptor expression (ER)	Negative / Positive	2.8
Progesterone receptor expression (PR)	Negative / Positive	2.9
Hormone receptor expression (ER_PR)	Pos_Pos / Pos_Neg / Neg_Pos / Neg_Neg	2.9
Histopathological tumour grading (Nottingham grade or Bloom-Richardson scale)	Good / Moderate / Poor	3.0
Herceptin2 expression status	Negative / Positive	22.6
Distal metastasis status*	None / Present	25.2
Nodal status	None / Present	11.3
Tumour size	<=2cm / >2cm	5.4
Tumour stage	I / II / III / IV	6.3
Diagnostic and therapeutic procedures		
Hospital setting	Public / Private	5.2
Method of tumour detection	Screening / Other	7.0
Type of surgery	Breast conserving / Mastectomy	7.1
Margins for invasive tumour component	<10mm / ≥10mm	6.6
Axillary dissection	Performed / Not performed	1.1
Adjuvant radiotherapy	Performed / Not performed	6.4
Adjuvant chemotherapy#	Performed / Not performed	66.0
Adjuvant hormone therapy	Performed / Not performed	27.6

* Missing metastasis status was assumed to represent M0
# Excluded from hazard regression analysis due to high levels of missingness

References

1. Protani, Coory and Martin (2010). *Breast Cancer Res Treat* 123, 627ff.
2. Parekh, Chandran and Bandera (2012). *Annu. Rev. Nutr*. 32: 311ff.

Conclusions

- The relative hazard of obese patients was compatible with inferior survival after adjusting for patient age and tumour stage, although not reaching statistical significance. It remained elevated also in the fully adjusted model. This is consistent with obesity effects via factors not accounted for in our study (e.g. metabolic syndrome; Ref. 2).
- There was indication of effect modification because obesity seemed to impair survival more in postmenopausal patients or those with lower stage tumours, although not reaching statistical significance.
- Findings were generally more pronounced in ductal vs all histology types.
- Effect sizes in the incomplete dataset were not sensitive to multiple imputation of likely values for missing observations. This argues against a strong bias in the inferences derived from the incomplete dataset.

Results 1: Associations of exposures with obese patients

Table 1: Patient, Tumour and Treatment characteristics of Breast cancer patients diagnosed in 2003-05 in Cantons Zürich and Basel
BMI < 30 (control), BMI ≥ 30 (case)

	All Histologies (N = 989)							Ductal Histology (N = 708)						
	BMI_miss		Control		Obese		X^2 Test	OR_{unadj} (95% CI) obese vs control	BMI_miss		Control		Obese		X^2 Test	OR_{unadj} (95% CI) obese vs control
Risk factor	N	%	N	%	N	%			N	%	N	%	N	%		
PATIENT CHARACTERISTICS																
Registry																
BA#	75	40.5	355	52.1	62	50.8		ref.	56	45.5	256	51.7	49	54.4		ref.
ZH#	110	59.5	327	47.9	60	49.2	0.800	1.05 (0.72-1.55)	67	54.5	239	48.3	41	45.6	0.634	0.90 (0.57-1.41)
Health Insurance Type																
basic	30	16.2	397	58.2	83	68.0		ref.	23	18.7	295	59.6	64	71.1		ref.
private	43	23.2	280	41.1	38	31.1	**0.039**	**0.65 (0.43-0.98)**	27	22.0	197	39.8	26	28.9	**0.045**	**0.61 (0.37-0.99)**
unknown	112	60.5	5	0.7	1	0.8			73	59.3	3	0.6	0	0.0		
TUMOUR CHARACTERISTICS																
Progesteron receptor status																
neg	64	34.6	268	39.3	35	28.7		ref.	45	36.6	206	41.6	27	30.0		ref.
pos	112	60.5	398	58.4	84	68.9	**0.025**	**1.62 (1.06-2.47)**	75	61.0	278	56.2	62	68.9	**0.031**	**1.70 (1.05-2.77)**
unknown	9	4.9	16	2.3	3	2.5			3	2.4	11	2.2	1	1.1		
Her-2 expression																
not amplified	91	49.2	448	65.7	88	72.1		ref.	63	51.2	327	66.1	65	72.2		ref.
amplified	19	10.3	109	16.0	11	9.0	**0.045**	**0.51 (0.27-0.99)**	15	12.2	89	18.0	7	7.8	**0.021**	**0.40 (0.18-0.89)**
unknown	75	40.5	125	18.3	23	18.9			45	36.6	79	16.0	18	20.0		
Stage																
I	55	29.7	232	34.0	35	28.7		ref.	37	30.1	169	34.1	22	24.4		ref.
II	67	36.2	286	41.9	54	44.3		1.25 (0.79-1.98)	49	39.8	204	41.2	42	46.7		1.58 (0.91-2.75)
III	26	14.1	117	17.2	19	15.6		1.08 (0.59-1.96)	17	13.8	89	18.0	15	16.7		1.30 (0.64-2.62)
IV	9	4.9	17	2.5	10	8.2	**0.011**	**3.90 (1.65-9.20)**	6	4.9	12	2.4	7	7.8	**0.023**	**4.48 (1.60-12.6)**
unknown	28	15.1	30	4.4	4	3.3			14	11.4	21	4.2	4	4.4		
TREATMENT CHARACTERISTICS																
Hospital setting																
public	63	34.1	394	57.8	85	68.0		ref.	43	35.0	297	60.0	64	71.1		ref.
private	95	51.4	269	39.4	32	25.6	**0.007**	**0.55 (0.36-0.85)**	66	53.7	185	37.4	24	26.7	**0.047**	**0.60 (0.36-0.996)**
unknown	27	14.6	19	2.8	8	6.4			14	11.4	13	2.6	2	2.2		
Margins (invasive)																
< 10 mm	111	60.0	490	71.8	60	49.2		ref.	78	63.4	361	72.9	46	51.1		ref.
≥ 10 mm	37	20.0	170	24.9	56	45.9	**< 0.001**	**2.69 (1.80-4.02)**	25	20.3	121	24.4	41	45.6	**< 0.001**	**2.66 (1.66-4.24)**
unknown	37	20.0	22	3.2	6	4.9			20	16.3	13	2.6	3	3.3		

#: survival time < 91.3 days *: expected cell frequency < 5

- Obese patients had significantly less often private health insurance.
- Obese patients had more often progesterone receptor-positive (PR+) and less often Her2-neu receptor expressing tumours.
- Obese women were significantly more often diagnosed with metastatic disease.
- After the first surgical intervention obese women had more often larger margins (≥ 10 mm) than non-obese.
- Obese patients did not differ from non-obese in relation to age, menopausal status and family risk for breast cancer, histological type and tumour grade, the screening-detected fraction and surgery type, axillary dissection, radiotherapy, chemotherapy and hormone therapy were equally performed in the two groups.

Results 2: Effects of exposures on survival of obese patients

Tab. 2 Excess hazard rate ratios and 95% confidence intervals (CI) of obese breast cancer patients. Obese (BMI ≥ 30) vs control (BMI < 30).

	Unimputed dataset				Imputed dataset	
	HR obesity (CI) all histologies	**P value**	**HR obesity (CI)** ductal	**P value**	**HR obesity (CI)** ductal	**P value**
Unadjusted model	2.10 (1.22-3.63)	0.008	2.60 (1.44-4.68)	0.001	2.45 (1.26-4.74)	0.009
Adjusted models						
Age and Stage	1.52 (0.85-2.74)	0.162	1.78 (0.91-3.48)	0.090	1.80 (0.95-3.44)	0.07
Fully adjusted [1]	1.51 (0.73-3.10)	0.265	1.71 (0.75-3.87)	0.198	1.77 (0.77-4.08)	0.177
Stratified analyses: Age(Menopausal status) [1]						
Premenopausal	0.31 (0.03-2.63)	0.280	no convergence [2]		0.61 (0.04-9.23)	0.724
Postmenopausal	2.26 (0.91-5.59)	0.077	2.70 (1.05-6.70)	0.039	2.24 (0.74-6.83)	0.115
Stratifier excluded	1.55 (0.79-3.16)	0.235	1.78 (0.79-3.99)	0.161	1.77 (0.77-4.08)	0.181
Stage [1, #]						
I/II	2.92 (0.86-9.85)	0.084	7.30 (1.25-40.5)	0.027	8.11 (0.81-81.1)	0.075
III/IV	1.39 (0.56-3.45)	0.473	1.49 (0.48-3.35)	0.429	1.54 (0.60-3.93)	0.369
Stratifier excluded	1.80 (0.92-3.48)	0.085	2.89 (1.42-5.9)	0.004	2.31 (1.07-5.7)	0.031
ER status [1]						
ER-neg	1.77 (0.42-7.42)	0.437	1.87 (0.40-8.81)	0.427	1.15 (0.17-7.87)	0.886
ER-pos	1.32 (0.50-3.70)	0.576	1.40 (0.50-3.93)	0.526	1.53 (0.49-7.75)	0.456
Stratifier excluded	1.46 (0.78-2.75)	0.240	1.95 (0.95-4.02)	0.070	1.70 (0.72-3.99)	0.231
PR status [1]						
PR-neg	2.62 (0.97-7.11)	0.058	2.07 (0.68-6.3)	0.200	1.84 (0.48-6.84)	0.366
PR-pos	1.25 (0.26-6.00)	0.770	2.80 (0.56-13.9)	0.209	2.76 (0.18-42.2)	0.465
Stratifier excluded	1.53 (0.81-2.9)	0.188	2.10 (1.03-4.3)	0.042	1.68 (0.70-4.02)	0.224

[1] Adjusted for age, stage, insurance, hormone receptors, Her2 receptor, grade, surgery, radiotherapy, hormontherapy, axillary dissection, margins(inv), hospital setting. Stratification variable excluded in stratified analyses and age replaced by proxy for menopause.

[2] Sparse data

- The excess hazard rate (or death rate relative to general population) in obese patients was 2-3 times higher compared with non-obese patients if no adjustments for other prognostic factors were made. After adjustments, it remained elevated.
- The inferior survival was more pronounced in the subgroup of ductal breast cancer.
- The effect sizes in different strata of presently discussed prognostic factors were elevated in postmenopausal women and for low-stage tumours.