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► **To cite this version:**

Å Olsson, Jp Garne, I Tengrup, S Zackrisson, J Manjer. Body Mass Index and breast cancer survival in relation to the introduction of mammographic screening. *EJSO - European Journal of Surgical Oncology*, 2009, 35 (12), pp.1261. 10.1016/j.ejso.2009.04.012 . hal-00556303

HAL Id: hal-00556303

<https://hal.science/hal-00556303>

Submitted on 16 Jan 2011

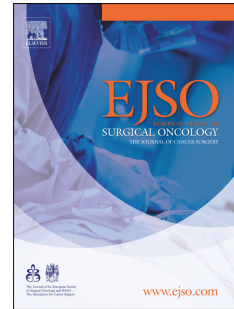
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Accepted Manuscript

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PII: S0748-7983(09)00159-0

DOI: [10.1016/j.ejso.2009.04.012](https://doi.org/10.1016/j.ejso.2009.04.012)

Reference: YEJSO 2832

To appear in: *European Journal of Surgical Oncology*

Received Date: 22 December 2008

Revised Date: 24 April 2009

Accepted Date: 30 April 2009

Please cite this article as: Olsson Å, Garne JP, Tengrup I, Zackrisson S, Manjer J. Body Mass Index and breast cancer survival in relation to the introduction of mammographic screening, *European Journal of Surgical Oncology* (2009), doi: 10.1016/j.ejso.2009.04.012

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Body Mass Index and breast cancer survival in relation to the introduction of mammographic screening

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Abstract

Aims: Mammographic screening reduces mortality in breast cancer. It is not known if this reduction is more pronounced in certain groups. Obesity has been associated with worse survival following breast cancer diagnosis. This study investigates BMI in relation to breast cancer mortality, and if this association is affected by invitation to mammographic screening.

Methods: In 1976, a randomised mammographic screening trial, inviting 50% of all women aged 45-69 years (n= 42 283), was set up in Malmö, Sweden. BMI in relation to breast cancer mortality was examined separately in women invited or not invited to screening in the trial. The analyses also included a historical control-group diagnosed before the screening trial. The study included 2974 women diagnosed 1961-1991. Relative risks (RR) with a 95% confidence interval was obtained from a Cox proportional hazard analysis and in the analysis of all women, follow-up was limited to 10 years.

Results: Obese women (BMI \geq 30) not invited to mammographic screening had a higher adjusted RR of dying of breast cancer as compared to normal weight women (2.08:1.13-3.81) in the 10-year follow-up. In women invited to screening there was no association between BMI and breast cancer mortality. In the historical control group, mortality was increased in overweight women (BMI: 25-30), RR=1.27:0.99-1.62, and obese women, RR=1.32:0.94-1.84, but these associations totally disappeared in the multivariate analysis, following adjustment for tumour size and stage.

Conclusions: Overweight and obese women may be a group that profit from mammographic screening to more than normal weight women.

Keywords: breast cancer, obesity, mortality, mammographic screening trial

Introduction

Mammographic screening reduces mortality in breast cancer. [1- 3] It is not known if this reduction is more pronounced in some groups, e.g. obese women.

Obesity has been associated with poor survival after breast cancer diagnosis. [4- 9] There are several mechanisms by which obesity can affect breast cancer survival. Hormonal and metabolic factors in obese patients may enhance tumour promotion [10, 11] and a selection of more aggressive tumour cells (clones) in the obese [9, 12] is another possible explanation. Apart from biological explanations obese women could present with larger tumours and more advanced disease due to delay of detection. In clinical studies it is difficult to separate the possible biological impact of obesity from factors concerning the problem of palpating a small lump in a big breast. The issue of detection difficulties has often been discussed but is, from a methodological point of view difficult to study.

One factor related to time of detection is mammographic screening. It is not known whether invitation to mammographic screening affects the potential association between BMI and breast cancer survival.

We have previously found high BMI (>25) to be associated with large tumour size and axillary lymph node involvement (ALNI) in women diagnosed with invasive breast cancer in Malmö, Sweden between 1961 and 1991. (Olsson et al, submitted for publication). However, in women invited to mammography in a randomised screening trial during the same period, the relation between BMI and tumour size was weak and there was no association between BMI and ALNI. According to these results, mammographic screening seems to be of greater importance for overweight and obese women concerning early tumour detection. The aim of this study was to evaluate the prognostic significance of our previous findings by examining BMI in relation to breast cancer mortality, and to investigate if this relation is affected by introduction of mammographic screening.

aterials and methods

The Malmö Breast Cancer Database

The Malmö University Hospital is the only hospital in Malmö treating women with breast cancer. The study-cohort consists of all cases of invasive female breast cancer in Malmö diagnosed between 1 Jan. 1961 and 31 Dec. 1991. Patients were retrieved by record linkage with the Swedish Cancer Registry and review of clinical notes, which rendered 4604 events of invasive breast cancer in 4453 women. A second linkage to the Swedish Cancer Registry was done in 2006.

Information was collected from clinical notes, histopathological examinations and the Swedish Cancer Registry by one single surgeon who also validated all breast cancer diagnoses. Data were extracted concerning date of diagnosis, height (cm), weight (kg), laterality (left, right or bilateral), tumour location (specific quadrant or central), type of surgery (mastectomy or local excision, with or without resection of axillary lymph nodes), distant metastases at diagnosis (yes or no) and menopausal status. A woman was considered postmenopausal if her menstruations had ceased more than 12 months prior to diagnosis, or, if this was unknown, if she was more than 50 years of age. All other women were considered pre/perimenopausal. All data are readily available in The Malmö Breast Cancer Database.[13] The present study was approved by the regional ethical committee (LU- Dnr 615/2004).

The Malmö Mammographic Screening Trial

The Malmö Mammographic Screening Trial, MMST, was a randomised, controlled trial that started in 1976. All women born in the period 1908-32 (n=42 283) and living in Malmö were randomly allocated to invitation to screening with mammography or no screening (controls). The trial ended in 1986 and was reported in 1988. [1] The randomised design was however maintained for almost five years after the end of the original trial in women up to age 70 or

until 1990. In 1990, the general service-screening programme started, and from that date all women aged 50-69 years have subsequently been invited regularly to mammography. [14] Women included in the invited and the control groups in the MMST can be identified in the Malmö Breast Cancer Database, but there is no information on individual screening participation.

Tumour characteristics and axillary lymph node involvement (ALNI)

Information about tumour size, histology and lymph node status was retrieved from histopathological examinations. For 111 inoperable patients, this information was retrieved by best available method, i.e. clinical, radiological or cytological examination. Between 1981-91 the histological classification used was a modification of the WHO's classification as proposed by Linell. [15] Tumour samples from 1961-1970 have been re-evaluated by one pathologist in order to re-classify these tumours according to this system. No information on histological subtype was available for cases diagnosed 1971-80. However, these tumours were reviewed if invasive/in situ status was uncertain and histological type has been given as "invasive, type not assessed". [13] Women operated in the axilla were classified as ALNI negative or positive according to the histopathological examination, or unknown, if no axillary dissection had been performed.

Body mass index (BMI)

BMI was calculated as kg/m^2 using information from clinical notes at time of diagnosis. Up until 1982, most patients were weighed and measured by a trained nurse, but from 1982 and onwards this information was often self-reported (personal communication, JP Garne, 18 Jan 2007). In the analyses, BMI was divided into four categories (<20 , $20-<25$, $25-<30$, ≥ 30).

Patients with unknown BMI (n=885) were included as a separate class in all the analyses.

Study population

Out of 4453 patients, 10 patients were excluded due to absence of clinical information other than diagnosis as were 109 women previously treated for breast cancer. Since the aim of this study was to examine survival, 111 patients with date of diagnosis same as date of death were excluded along with 104 subjects with bilateral cancer. Invitation to MMST started in October 1976, but most women in the invited group did not receive an invitation until 1977, hence, invitation to screening was considered to have started in 1977. Of women with invasive breast cancer in the Malmö Breast Cancer Data Base, 656 women had been invited to screening in the MMST, and 570 patients had been randomised to the control group. The present analysis also includes a historical control group (hereafter referred to as the pre-screening group) of 1568 subjects diagnosed before 1977, but with the same diagnostic age as controls within the MMST. The final study population included 2794 individuals.

Breast cancer mortality

Information of cause of death was received from the Swedish Cause of Death Registry (latest update on 31 December 2004) [16] and was classified as death of breast cancer, breast cancer as multiple cause of death, death of other causes, or alive, i.e. if not registered as dead 10 years after diagnosis.

Statistical methods

All women included in MMST were followed from diagnosis until death or up to 10 years after diagnosis. The main outcome in the present study was breast cancer as underlying cause of death, not including breast cancer as multiple cause of death. Breast cancer mortality was calculated per 100 000 person years in different categories of BMI. Corresponding relative risks were obtained using a Cox proportional hazard analysis. Adjustment was made for potential

prognostic factors available in the Malmö Breast Cancer Database yielding crude and adjusted relative risks (RR) with 95 % confidence intervals (CI). Since initial analyses indicated a non-linear association between BMI and breast cancer mortality, 4 BMI categories were used (<20, 20-<25, 25-<30), ≥30). In all the analyses the second BMI-category (20-<25) was used as reference. All analyses were repeated excluding patients inoperable due to advanced tumours (n=120), patients with distant metastases at diagnosis (n=259), and women inoperable due to other disease than breast cancer (n=75). SPSS 13.0 was used for all calculations.

Results

Patient characteristics with reference to BMI

Women with a high BMI (>25) were older and more often postmenopausal than were lean women, table 1. This group also had larger tumours. The distribution of other covariates was similar in different BMI categories. Women with no information on BMI had a high percentage of distant metastases at diagnosis; they were relatively old and had a large proportion of missing values regarding most tumour characteristics, table 1.

Mortality with reference to BMI and mammographic screening

In women not invited to screening (controls) a significantly higher relative risk of breast cancer death was seen in both the highest and the lowest BMI categories table 2. In the screening group, a statistically significant, elevated risk was seen in the lowest category of BMI, while no increased risk was seen in the highest BMI category, table 2. Obese and overweight women in the pre-screening group had a statistically non-significant increased risk of breast cancer death, which disappeared in the multivariate analysis including age at diagnosis, menopausal status and information on tumour characteristics, table 2.

In all analyses, breast cancer mortality was significantly higher among women with unknown BMI. Results remained similar after exclusions of subjects inoperable due to advanced tumours, subjects with distant metastases at diagnosis and patients inoperable due to other disease than the breast cancer, (data not shown).

Discussion

Among women not invited to screening, there was a positive association between BMI and breast cancer mortality in the highest and lowest BMI-classes. In women invited to screening, there was an association between low BMI and breast cancer mortality, while high BMI was not associated with mortality.

Previous studies

Many previous studies show a positive association between overweight/obesity, mostly measured as BMI, and mortality in breast cancer patients. [4-9] In an extensive review by Chlebowski in 2002, including 159 references, the author concludes that women with breast cancer who are overweight or who gain weight after diagnosis have a greater risk of breast cancer recurrence and death compared to normal weight women. [4] This has also been further confirmed in large, more recent studies. [5-9] In our study, high BMI was positively associated with breast cancer mortality only in the control group not invited to mammography screening in the MMST, despite a large number of breast cancer cases and a long follow-up.

At least five studies report no association between overweight/obesity and mortality in breast cancer patients. [17-21] Except for the study by den Tonkelaar [21], the proportion of screening detected tumours in these studies was not given.

The influence of BMI and screening on survival

We found only two studies on BMI and breast cancer mortality in relation to mammographic screening. A study by den Tonkelaar et al. examined subcutaneous fat patterning and BMI with reference to survival in 241 postmenopausal women with invasive breast cancer retrieved from a population based breast cancer screening project including 14 697 women. [21]. They did not find any association between any anthropometric measures and survival. In a study of 89 835

volunteer women participating in the Canadian Breast Screening Study, triceps skin fold thickness, but not BMI, was associated with worse survival in 1033 breast cancer cases.

Mortality was not affected by allocation to mammography in their study. [22]

In our study, there seems to be a u-shaped association between BMI and breast cancer mortality. This have indeed been described by others, [19, 23] while other find no such association. [6-8] Studies using 2 BMI categories, with a cut off somewhere in the middle, will fail to detect a potential over-risk in underweight women.

Methodological issues

Some methodological issues have to be considered. All women in Malmö were included in this study and they were all treated at the same hospital. The randomisation in MMST was strictly population based. This diminishes the risk of a potential selection bias. All cases were retrospectively reviewed by one surgeon increasing the validity of the breast cancer diagnosis.

Reliability of BMI data

In this study, patients in the first part of the study period were weighed and measured by trained nurses, while this information from 1982 and onwards was mainly self-reported. It had been desirable to have these anthropometrical measures collected in the same way throughout the study period. Several studies have reported a tendency for overweight subjects to overestimate height, and to underestimate weight, resulting in an underestimation of BMI while underweight individuals tend to overestimate weight. [24-26] If this is valid for our population, it would have attenuated the observed risks, but any such tendency is unlikely to have been influenced by invitation to mammographic screening. Several reports describe weight gain after breast cancer diagnosis and there is also evidence that such weight gain has adverse prognostic impact on both disease free survival and mortality. [4] The Malmö Breast Cancer Data Base includes BMI

at baseline, but offers no information on weight changes over time but it is unlikely that a subsequent weight gain would be affected by screening mammography. Moreover, BMI at diagnosis may indeed be the most relevant measurement from a clinical point of view; this will allow the identification of women that may profit from intensified treatment or follow-up.

Women with unknown BMI were analysed as a separate category. Generally they were older, had a higher percentage of distant metastases at diagnosis and they had an increased relative risk of dying of breast cancer. Despite adjustment for age and distant metastasis at diagnosis, the observed association persisted. However, these women had missing information on most tumour characteristics, and there may be some residual confounding in this group.

Reliability of survival data

The validity of information on cause of death in breast cancer patients has previously been investigated in Malmö and was found to be high.[1] All included subjects have been followed for at least 12 years and the national registry is of good quality.[16] We therefore used breast cancer as cause of death instead of the more commonly used, all cause mortality, as this is probably a more relevant end-point.

Confounding factors influencing on survival

Adjustment was made for age, menopausal status, histology, laterality, tumour size class, distant metastases at diagnosis and tumour location. These factors ought not to have affected the results. In the analyses at 10 years of follow up, including the pre-screening group, there was a similar pattern in the pre-screening group and in women not invited to screening in the MMST. However, the association between obesity and poor survival in the pre-screening group totally disappeared following adjustments for tumour characteristics. Adjustment was made for diagnostic period within each strata of screening status, but considering the long period of

inclusion, and possible changes in principles for diagnosis and treatment, these results must be interpreted with caution.

This study has some limitations. No information on tumour characteristics other than tumour size and axillary lymph node status was available. Specific tumour characteristics affect mortality and could be related to BMI. Indeed, in a study of 1177 premenopausal women, examining tumours larger than 20mm, Daling et al. found that the heaviest women were more likely to have tumour characteristics associated with poor survival. [9]

Another problem in the present study is the lack of information on non-surgical treatment. Antioestrogens were introduced during the study period and if the screening and the control group differ in receptor status and antioestrogene treatment, this could have affected the results. The decision to use other adjuvant therapy was based on factors such as age, menopausal status, tumour size and axillary lymph node status. Probably, adjustments for these factors would have diminished a potentially confounding effect of adjuvant therapy. There was no information on life-style factors such as smoking, use of alcohol, dietary fat intake, education, marital status or the use of Hormone Replacement Therapy (HRT). It is however, unlikely that such factors would differ by invitation to screening.

Reverse causality

Women with missing values, and inoperable patients, were all included in order to have as unselected a population as possible. It is possible that the disease itself would have affected BMI, in patients with distant metastases at diagnosis and in patients inoperable due to advanced tumour. On the other hand, subjects inoperable due to other disease than breast cancer could have had changes in body weight not related to breast cancer. When all analyses were repeated separately excluding these groups, results remained similar.

The mammographic screening status

In this material we cannot identify which women among controls that received examination with mammography outside the screening trial. However, we know that about 20 % of screening controls had subsequent tumours detected by mammography. Out of all invited women, 74% attended the first examination and the following examination rate was 70%. [1] Misclassification with respect to way of detection would have lead to an underestimation of the effect of mammographic screening on the relation between BMI and breast cancer mortality. Participation in mammographic screening could be BMI-dependent, but previous reports have not been consistent. [12, 27-31] In this study we were able to investigate women invited to screening as a group which corresponds to an “intention-to-treat-approach”. This may indeed be useful considering the impact of invitation to mammographic screening as a preventive tool.

Mammography has the same sensitivity regardless of BMI, but lower specificity for obese women, [27] and such differences are not likely to explain the results in the present study.

Conclusion

This study reports a difference in breast cancer mortality in obese women randomized to mammographic screening or not. It is possible that overweight and obese women benefit more from mammographic screening than normal weight women.

Acknowledgments

Financial support was received from The Ernhold Lundström Foundation, The Einar and Inga Nilsson Foundation, The Malmö University Hospital Cancer Research Fund, The Malmö

University Hospital Funds and Donations, The Crafoord Foundation, The Anna Lisa and Sven-Eric Lundgren Foundation, and The Mossfelt Foundation.

Conflict of interest

The authors state that they have no conflict of interest.

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Table 1. Distribution of BMI in relation to age, menopausal status and tumour characteristics.

Factor	BMI				
	< 20 (n= 146)	20- <25 (n= 859)	25- <30 (n= 648)	≥ 30 (n= 256)	Unknown (n= 885)
	Column percent <i>Mean and standard deviations in italics</i>				
Age at diagnosis (years)*	61.4 (9.8)	61.6 (9.4)	64.4 (8.7)	65.1 (8.0)	63.6 (9.8)
Menopausal status					
premenopausal	18	18	10	9	14
postmenopausal	82	82	90	91	86
Size of primary tumour (mm)					
0-≤5	2	3	2	3	2
>5-≤10	21	15	14	12	10
>10-≤20	31	33	32	32	27
>20-≤50	17	23	29	32	25
>50	0	2	4	7	5
Unknown	29	25	18	15	30
Axillary lymph node status					
Negative	57	56	43	54	38
Positive	33	37	49	42	37
Unknown	10	7	8	4	25
Histological type					
tubular (++++,+++)	12	10	8	10	2
tubuloductal (++,+,0)	16	20	2	19	5
comedo	34	32	33	34	12
lobular	13	11	9	11	4
invasive, varia, unknown	9	11	13	12	9
invasive, type not assessed	17	16	14	13	68
Tumour location					
UIQ	12	18	20	24	17
LIQ	6	6	8	6	8
UOQ	49	44	42	37	39
LOQ	12	11	12	12	14
Central	15	15	15	17	13
Unknown	6	6	4	4	9
Distant metastasis at diagnosis					
No	96	97	96	96	89
Yes	4	3	4	4	11
Unknown	0	0	0	0	0
Diagnostic period					
1961-70	47	40	42	37	14
1971-80	26	23	21	17	74
1981-91	27	37	36	46	12

Table 2. BMI in relation to breast cancer mortality with stratification for screening status.

Screening-status	BMI	Subjects (n)	Breast cancer deaths (all deaths)	Person-years	Breast Cancer mortality/100 000	Relative Risk (95% CI)	Relative Risk* (95% CI)
Pre-screening [‡]	< 20	90	26 (47)	1190	2185	0.98 (0.64-1.49)	1.41 (0.92-2.15)
	20-< 25	419	134 (201)	6210	2158	1.00	1.00
	25-< 30	330	124 (195)	3849	3222	1.27 (0.99-1.62)	1.06 (0.82-1.36)
	≥ 30	115	45 (64)	1233	3650	1.32 (0.94-1.84)	1.04 (0.74-1.47)
	Unknown	614	235 (355)	6762	3475	1.30 (1.05-1.60)	1.29 (1.00-1.66)
	All	1568	564 (862)	19 244	2931		
Invited to screening	< 20	22	5 (6)	348	1437	2.04 (0.78-5.32)	3.09 (1.14-8.38)
	20-< 25	240	26 (64)	3482	747	1.00	1.00
	25-< 30	171	19 (37)	2531	751	1.02 (0.57-1.85)	1.52 (0.82-2.84)
	≥ 30	76	6 (18)	1072	560	0.73 (0.30-1.77)	1.01 (0.41-2.50)
	Unknown	147	55 (85)	1534	3585	4.41 (2.76-7.03)	3.02 (1.72-5.32)
	All	656	11 (210)	8967	1238		
Controls	< 20	34	10 (16)	376	2660	2.87 (1.38-5.95)	2.71 (1.28-5.72)
	20-< 25	200	26 (58)	2767	940	1.00	1.00
	25-< 30	147	35 (57)	1893	1849	1.90 (1.15-3.16)	1.27 (0.75-2.15)
	≥ 30	65	20 (28)	702	2849	2.62 (1.46-4.70)	2.08 (1.13-3.81)
	Unknown	124	51 (87)	1061	4807	4.59 (2.86-7.37)	1.76 (1.00-3.08)
	All	570	142 (246)	6799	2088		

*Adjusted for age at diagnosis (continuous), menopausal status, histological type, tumour size class, diagnostic period, axillary lymph node status, tumour location, and distant metastasis. [‡]With diagnostic year < 1977 and same diagnostic age as screening subjects and controls.