



EFFECT OF BODY MASS INDEX ON RECURRENCE IN BREAST CANCER PATIENTS

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ABSTRACT:

BACKGROUND: Breast cancer is the most common cancer among European and North American or “Western” women. More than half of all patients diagnosed with breast cancer are obese. An association between obesity and risk of primary breast cancer has already been established and a Body Mass Index (BMI) higher than 35 is associated with worse disease-free survival. As weight gain is common during treatment, the percentage of obese patients is even larger after becoming disease-free.

OBJECTIVE: To examine if postmenopausal Western breast cancer patients are more susceptible to cancer recurrence when they are overweight or obese.

METHODS: We performed a systematic literature review and meta-analysis. We searched PubMed and Embase for articles related to recurrence, breast cancer and obesity. We excluded articles when no full text was available and articles which did not use relative risk (RR) as outcome measure. Reviews were not immediately excluded; instead we searched their references for primary studies.

RESULTS: The search yielded seventeen articles, after critical appraisal we included four studies in our meta-analysis. All included studies reported a positive association between risk of breast cancer recurrence and BMI. Compared to normal-weight women, overweight and obese women have a higher risk of recurrence. Our results show a recurrence of 14.3% in non-obese patients, 16.5% in overweight patients and 18.5% in obese patients. This means there are an additional 42 recurrences for every 1,000 obese breast cancer patients. This amounts to a relative risk of 1.13 (95%CI: 1.02-1.24) and 1.27 (95%CI: 1.14-1.41), respectively.

CONCLUSION: Our meta analysis showed that both being overweight and obese are risk factors for recurrence in BC patients. We hypothesise that reducing BMI will lead to lower breast cancer recurrence. Therapies directed at losing weight could become a standard after-treatment procedure for obese people, who are at higher risk for breast cancer recurrence.

WHAT'S KNOWN: Obesity is a medical condition and a growing problem in the Western world, associated with type II diabetes and metabolic syndrome, among other pathologies. An association between obesity and risk of primary breast cancer has been established and a BMI higher than 35 is associated with worse disease free survival.

WHAT'S NEW: Overweight women are at increased risk for recurrence of breast cancer. It is advised to strive for a healthy weight in the treatment of breast cancer and reducing the risk of recurrence.

KEYWORDS: Obesity, breast cancer, recurrence, postmenopausal

Introduction

Breast cancer is the most common cancer among women, especially in the Western population. One in eight Dutch females are diagnosed with breast cancer at some point in their life and 3,200 women die of breast cancer each year. 75% of people diagnosed with breast cancer are over 50 years old [1]. Because of the national screening program for breast cancer smaller tumours are detected and, together with improved treatment, mortality has decreased [2]. The 10 year survival rate for women with breast cancer is 70% and increasing [2,3].

Most patients diagnosed with early stage breast cancer will undergo either a lumpectomy or mastectomy followed by local or systemic therapy, sometimes combined with radiation therapy. The choice of treatment depends on the grade and size of the tumour, involvement of the lymph nodes, hormone sensitivity and general health of the patient [4].

After successful treatment, the probability of breast cancer recurrence varies greatly between individuals. Positive lymph nodes, premenopausal tumours and triple negative tumours are all examples of factors that give poorer prognosis [4,5]. However, the patient has no influence over these factors, unlike their control over their body weight.

Body weight is partly determined genetically, but diet and physical activity have a large influence [5]. A person is considered overweight with

a BMI >25 kg/m² and is considered obese with a BMI >30 kg/m² as defined by the World Health Organization (WHO). We defined non-obese as a BMI <25 kg/m². Obesity is a medical condition and a growing problem in the Western world, associated with type II diabetes and metabolic syndrome, among other pathologies [5,6]. An association between obesity and risk of primary breast cancer has been established [2] and a BMI higher than 35 is associated with worse disease free survival [3]. A few potential mechanisms have been proposed: hyperinsulinaemia may help proliferation and invasion of potentially cancerous cells [7]. Adiposity causes higher blood concentrations of oestrogen, which may play an important role in hormone sensitive breast cancer [5]. More than half of all patients diagnosed with breast cancer are overweight or obese and weight gain is common during treatment [3,8].

The purpose of this study is to determine if postmenopausal Western breast cancer patients are more susceptible to cancer recurrence when they are overweight or obese compared to non-obese. All included patients were treated for primary breast cancer. We defined recurrence as a new local tumour or a metastasis. We considered someone overweight or obese as defined by the WHO and patients were considered postmenopausal when the menopause was a natural event. We included only postmenopausal women, because this reduces the confounding effect that hormone levels might have on the study.

Table 2 Critical Appraisal - RCT, randomised controlled trial; N, number of patients; BMI, two or three group separated by BMI; MR, BMI measured by researcher; CG, control group (normal BMI); LF, Length of follow-up (5-10yr =+; >10yr =++); LS, Loss to follow-up <20%; OU, recurrence is primary outcome; +, adequate; -, inadequate or unreported.

			Criteria					
Study	Design	N	BMI	MR	CG	LF	LS	OU
Ewertz et al, 2012 [9]	RCT	4760	+	-	+	+	+	-
Kamineni et al, 2012 [10]	Cohort	288	+	-	+	++	-	+
Robinson et al, 2014 [11]	Cohort	1155	+	-	+	+	-	+
Sestak et al, 2010 [12]	RCT	4933	+	?	+	-	-	+
Loi et al, 2005 [13]	Cohort	485	+	-	+	+	-	+
Majed et al, 2011 [14]	Cohort	15166	+	+	+	++	-	+

Table 1 Search Strategy.

Database	Search
Pubmed	("survival"[Mesh] OR survival[tiab] OR "Mortality"[Mesh] OR "neoplasm Recurrence, Local"[Mesh] OR recurrence[tiab]) AND ("Breast Neoplasms"[Majr] OR breast cancer[ti] OR breast neoplasms[ti] OR breast carcinoma[ti]) AND ("Overweight"[Mesh] OR body weight[tiab] OR obesity[tiab])
Embase	(Exp recurrence/ OR recurrence.ti.ab. OR Cancer recurrence.ti.ab. OR Relapse.ti.ab. OR Exp recidivism/ OR recidivism.ti.ab. OR recidive.ti.ab.) AND (Exp breast tumor/ OR breast tumor.ti.ab. OR breast neoplasm*.ti.ab. OR breast cancer.ti.ab.) AND (Exp obesity/ OR obesity.ti.ab. OR obese.ti.ab. OR overweight.ti.ab.)

Methods

The terms and synonyms we defined to be used in Embase and PubMed were based on the population: female postmenopausal breast cancer survivors; on the determinants: being overweight or obese; and on the outcome: recurrence. Our search strategy can be found in table 1.

After the search, we first removed duplicates, then we selected articles based on title and abstract and afterwards on full-text screening. We excluded studies if it was an animal study or included a non-western population. Articles were also excluded when we could not access the full text. Reviews were not immediately excluded; we searched their references

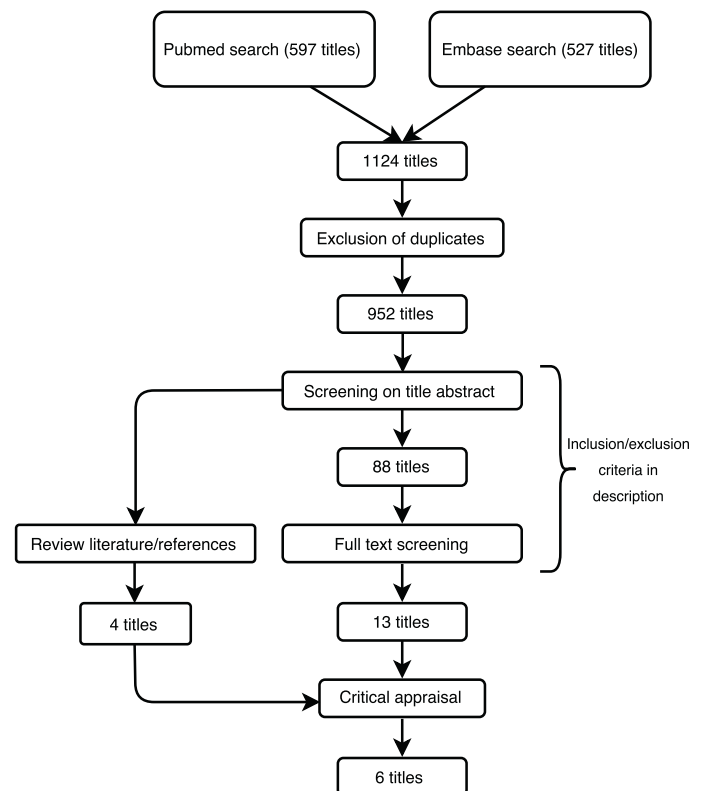


Figure 1 Flowchart of the search and appraisal process.

Inclusion criteria: Recurrence as primary outcome; Groups based on BMI.

Exclusion criteria: No full text; studies done before 2005; animal studies; non-western population; no follow-up.

Table 3 Meta-analysis of relative risk of BMI on recurrence of breast cancer - N: number of breast cancer patients; BMI<=25: incidence of recurrence in group with BMI below or equal to 25 during follow-up, same for other groups; RR overweight: relative risk of recurrence of BMI 25-30 group compared to BMI<25 group; RR obesity: relative risk of recurrence of BMI>30 group compared to BMI<25 group; Total: meta-analysis of the studies, weighted by number of patients. Recurrence is higher in patients that have a higher BMI. Both the relative risks for overweight and for obesity are significant.

Study	N	BMI <=25	BMI 25>=30	BMI >30	RR overweight	RR obesity
Ewertz	4760	16.1%	17.5%	18.3%	1.08[0.94-1.25]	1.14[0.97-1.34]
Kamineni	485	9.8%	10.0%	22.2%	1.03[0.56-1.90]	2.28[1.32-3.92]
Robinson	1155	6.4%	8.6%	12.7%	1.34[0.84-2.14]	1.98[1.25-3.14]
Sestak	4933	15.3%	17.7%	19.4%	1.16[1.00-1.34]	1.27[1.09-1.48]
Total [5]	11333	14.3%	16.5%	18.5%	1.13[1.02-1.24]	1.27[1.14-1.41]

instead and found four additional articles for the critical appraisal. Figure 1 shows a flowchart of how we included articles. All included articles contained either almost only postmenopausal women or stratified data for pre- and postmenopausal women.

Subsequently, we critically appraised the found articles based on the Newcastle-Ottawa scales for cohort studies, with which we compiled our own set of criteria, which was also relevant for randomised controlled trials (RCTs), to appraise the articles, which can be found in table 2. Finally, we performed a statistical analysis using the standard functions in the program Cochrane Review Manager, calculating RRs and heterogeneity between the studies. The studies used in this analysis were weighed by the number of patients included in those studies: studies with more patients contributed more to the result of the meta-analysis. By doing this we corrected for the size of the studies.

Results

Our initial search returned 597 articles from PubMed and 527 from Embase. Exclusion, removal of duplicates and inclusion of articles referenced yielded seventeen articles to enter the critical appraisal. This ultimately resulted in six articles to be used in our case report. The following articles were included in the meta-analysis; Ewertz et al. [9], Kamineni et al. [10], Robinson et al. [11] and Sestak et al. [12]. We could not determine the amount of breast cancer recurrences and

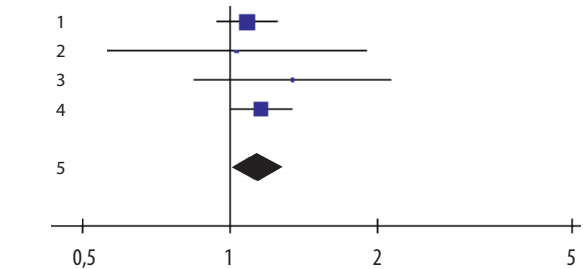


Figure 2 Forest plot of meta-analysis of relative risks of overweight in breast cancer patients on recurrence. 1- Ewertz et al., 2- Kamineni et al., 3- Robinson et al., 4- Sestak et al., 5- Pooled effect. The overall effect is significant. The studies are homogeneous ($P=0.80$; $I^2=0\%$).

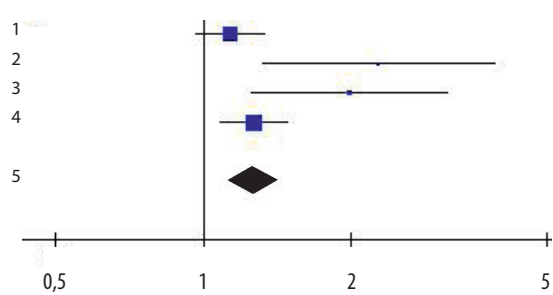


Figure 3 Forest plot of meta-analysis of relative risks of obesity in breast cancer patients on recurrence. 1- Ewertz et al., 2- Kamineni et al., 3- Robinson et al., 4- Sestak et al., 5- Pooled effect. The overall effect is strongly significant. The smaller studies show a larger effect; the studies are heterogeneous ($P=0.02$; $I^2=70\%$).

thus relative risk (RR) from the study by Loi et al. [13]; Majed et al. [14] only used contralateral breast cancer as an outcome measure. These studies were excluded from the meta-analysis.

The study of Ewertz et al. is an RCT in which the association between BMI and the risk of recurrence or death in postmenopausal women with breast cancer is examined. The patients received adjuvant tamoxifen or letrozole. Both drugs block oestrogen effects. In this study, 4,760 patients with early stage breast cancer were included. Breast cancer recurrence is a secondary outcome measure, with disease-free survival as primary outcome measure. The study did not find any significant results in outcome measures between treatment with tamoxifen or letrozole.

The study of Kamineni et al. reports that obesity may contribute to poorer breast cancer outcomes. A cohort design was used in which 485 women of over 40 years were included with stage I/II breast cancer. The primary outcome measure is breast cancer recurrence in the ipsilateral breast or distant recurrence after 120 days following the completion of the initial course of therapy.

Robinson et al. associates obesity with poorer invasive breast cancer prognosis. In this cohort study, 1,199 women were recruited (of which 296 were premenopausal) with a mean age of 58 years. The participants completed an enrolment questionnaire (completed between 8 and 58

weeks from diagnosis) and completed an annual follow-up questionnaire every 12 months for 5 years, in which they reported recurrence or new breast cancer. The outcome used is local or distant recurrence, new breast cancer, or death due to breast cancer.

The results of Sestak et al. confirm poorer prognosis of obese women with early stage breast cancer. This study is a double-blind RCT in which postmenopausal women with early-stage breast cancer were randomly assigned to receive anastrozole, which also blocks oestrogen effects, tamoxifen or the combination in a double-blind fashion. The impact of BMI on recurrence and the relative benefit of anastrozole versus tamoxifen according to baseline BMI were investigated. The primary outcome measure is recurrence. Obesity is not the primary determinant, but obesity was taken into account and included in the results.

Table 3 shows the results of the meta-analysis that was carried out. Our results are not weighted for person-years. Recurrence was found in 14.3% of patients with a BMI lower than 25 (healthy group), in 16.5% of patients with a BMI between 25 and 30 (overweight group), and in 18.5% of patients with a BMI higher than 30 (obese group). The RR of recurrence of the overweight group compared to the healthy group was significantly higher (RR= 1.13; 95%CI[1.02-1.24]; $p=0.02$). The RR in the obese group compared to the non-obese group was even higher and strongly significant (RR=1.27; 95%CI[1.14-1.41]; $p<0.0001$).

Figures 2 and 3 show a visual representation of the meta-analysis. It shows that the studies are homogeneous for overweight ($P=0.80$; $I^2=0\%$) but not for obesity ($P=0.02$; $I^2=70\%$); the smaller studies show a larger effect of obesity on breast cancer recurrence.

Discussion

According to the meta-analysis, the relative risk of recurrence in the overweight group is significantly higher compared to the normal BMI group (RR=1.13; 95%CI=[1.02-1.24]). For the obese patients, we see similar results (RR=1.27; 95%CI=[1.14-1.41]). Being overweight or obese is a potential risk factor for breast cancer recurrence based on these results.

The main strengths of our systematic review lie with the extensiveness of the search strategy and the critical appraisal. We searched both PubMed and Embase using a multitude of synonyms and in addition to that, we also searched the references of a number of systematic reviews. As a result, the chance of missing relevant studies was minimised. We identified one weakness in our search strategy: studies from before 2005 were not included because of the possibility of dated results. In retrospect, we should not have used this exclusion criterion because we did not have evidence to assume that results from studies before 2005 and after 2005 differ from each other. Besides that, if we had included studies from before 2005 in our search, we probably would have had included more articles in our analysis.

A limitation of our study lies with the published literature. Ideally, we would have preferred all the studies included to have measured the BMI of the patients after treatment, as chemotherapy may induce weight gain [15]. Had we known the weight of the women after treatment, we could potentially have demonstrated a larger effect than we have now. Secondly, three of the four included studies did not report recurrence for premenopausal and postmenopausal patients separated. However, the median age of women included was far beyond menopause in these studies. Ewertz et al. had a median age of 62, Kamineni et al. had a percentage of women below 50 of only 22%, Robinson et al. had a mean age of 58. Only Sestak et al. exclusively included postmenopausal women. Considering that some premenopausal women were included in

our analysis, our found effect may be smaller than it is in actuality. This is because obesity has been found to be a risk-lowering factor for premenopausal women [16]. Finally, we would have appreciated conformity in the outcome measures. As Kamineni et al. did not consider contralateral breast cancer as recurrence, our results might have been skewed. We had to exclude Majed et al. from our meta-analysis as they only looked at contralateral breast cancer recurrence.

A part of the heterogeneity between the included studies can be explained due to the difference in outcome measures. Another important factor in the heterogeneity is the difference in follow-up; the longer the follow-up, the larger the amount of recurrences. Ewertz had a median follow-up of 8.7 years, Kamineni used a follow-up of 10 years, Robinson used 5 years and Sestak had a median follow-up of 8.3 years. This implies that in the Kamineni study, the reported number of recurrences should be higher than in the other studies. This is true for a BMI >30.

A factor that could have confounded our results is the medication used in the randomized controlled trials we included. Letrozole was more effective than tamoxifen in all BMI groups in reducing breast cancer recurrences. Anastrozole was more effective as well, but had a greater effect in thin women than in obese women [9,12]. As such, the group receiving anastrozole may have contributed to a larger effect of obesity in our meta-analysis.

As all included studies reported a greater risk of breast cancer recurrence in obese women, the conclusion that obesity is in fact a risk factor for breast cancer recurrence is valid. The actual impact might slightly differ from our meta-analysis, as we identified both factors that might reduce or that might increase the actual effect. Due to confounding and variation in literature, it is hard to estimate the actual size of the effect. However, it is clear that there is an effect, as the meta-analysis shows a very strongly significant result and the relative risk of 1.27 is a good estimation of the effect.

According to several studies [16,17], obesity is a risk-reducing factor in premenopausal women whereas it increases the risk of contracting breast cancer in postmenopausal women. This is probably due to a hormonal mechanism that changes during menopause [18]. Similar to our study, Loi et al. found a positive correlation between obesity and breast cancer recurrence in postmenopausal women with a hazard ratio of 2.03 (95%CI: 0.99 – 4.21) [13]. In contrast to our results, Majed et al. found obesity to be a protective factor for contralateral breast cancer recurrence in postmenopausal women (RR=0.91; 95%CI: 0.75-1.11) [14]. This can be explained by the difference in outcome measures: contralateral breast cancer recurrence is only a small part of total recurrence.

We hypothesise that reducing BMI will lead to lower breast cancer recurrence and better life expectancy in general. As such, we would recommend a randomized controlled trial that divides postmenopausal obese breast cancer survivors in two groups; one receiving a weight loss intervention whereas the other group does not. Comparing the recurrence of breast cancer between these groups could show the value of such an intervention and could complement the outcome of our research. The cost of such an intervention programme could be weighed against the beneficial effects. As weight loss without an intervention programme is free of cost, a demonstrated effect in the RCT could add to the recommendation of losing weight. In turn, this could lead to changes in guidelines for postmenopausal breast cancer survivors; weight loss could become a standard after-treatment intervention programme for obese patients, who are highly at risk for a renewed episode of breast cancer, should it be cost-effective. In addition, we would advise medical professionals to better monitor the weight of breast cancer patients, both during

treatment and follow-up.

Conclusion

In conclusion, our results show a recurrence of 14.3% in non-obese patients and 18.5% in obese patients. This means there are an additional 42 recurrences in every 1,000 obese breast cancer patients. Something to keep in mind is that obesity is associated with a broad range of diseases, such as diabetes and cardiovascular diseases. Our results strengthen the recommendation to maintain a "healthy" BMI, preferably below 25, in order to decrease the risk of breast cancer.

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