REVIEW ARTICLE

The Effect of Overweight and Nutrition on Prognosis in Breast Cancer

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SUMMARY

Background: Breast cancer is the most common cancer in women. Body weight and nutrition are known to play an important role in its pathogenesis. The question thus arises whether lifestyle factors might influence the prognosis of breast cancer, potentially offering new approaches for secondary prevention.

Methods: We selectively searched the Medline database for all studies and meta-analyses on this topic that were published from 1966 to June 2010. We evaluated the cohort studies, interventional trials, and meta-analyses with respect to three target variables: tumor recurrence, tumor-specific mortality, and overall mortality.

Results: A high body-mass index (BMI) at the time of diagnosis of breast cancer is associated with higher overall mortality, as is weight gain at later times. A low-fat diet rich in fruit, vegetables, and fiber seems to be weakly associated with a better prognosis. On other hand, there is no evidence for any benefit from micronutrients, supplements, or antioxidant foods. Alcohol consumption does not affect the outcome in breast cancer. Two intervention trials of reduced fat intake showed no effect on survival, but the target of the intervention was not met in either trial.

Conclusion: The intervention trials yielded negative results. Nevertheless, in view of the methodological difficulties in this area of research and the overall life situation of women with breast cancer, the authors recommend a health-promoting lifestyle with avoidance of overweight and a low-fat diet rich in fruit, vegetables, and fiber.

In Germany, breast cancer is the most common cancer in women. Its annual incidence is around 58 000 new cases; 17 000 women die due to the cancer every year (1). The five-year survival rate is currently reported to be 83% to 87%. At the end of 2006, an estimated 242 000 women in Germany were living with a breast cancer diagnosis that they had received up to five years previously (1). The women's survival is vastly determined by tumor stage at diagnosis; women with early, non-metastasized tumors can be expected to have a good prognosis. In this sense, breast cancer is more and more assuming the characteristics of a chronic disease.

A report published in 2007 by the World Cancer Research Fund (WCRF) looked into the importance of body weight, nutrition, and physical activity in the development of tumor disease and which recommendations can be deduced from the findings in terms of primary prevention (2). This report and other publications raised a great deal of interest among physicians and cancer patients about the importance of lifestyle for the prognosis of breast cancer.

This review article aims to collect and critically evaluate current study results of the importance of body weight, weight gain, and nutrition for the prognosis of breast cancer, on the basis of a selective literature search.

Methods

After the search terms were defined and agreed, we conducted a PubMed search for the time period from 1966 to June 2010. The search terms we applied were "overweight AND breast cancer prognosis" and "overweight AND breast cancer survival". Similarly we combined the terms "obesity", "weight gain", "diet", "dietary factors", "micronutrients", "vitamins", "soy", "green tea", "selenium", "antioxidants" with "breast cancer survival" or "prognosis".

We included in the evaluation only prospective cohort studies and interventional studies, which we selected firstly on the basis of their abstract and then analyzed in total. Smaller cohort studies with fewer than 200 participants were excluded. We included systematic reviews and meta-analyses. Further studies and

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information were found in the reference lists of the identified studies.

The defined end points were tumor recurrence, breast cancer specific mortality, and all-cause mortality. We evaluated the studies in the basis of the methods used by the World Cancer Research Fund (2). The evidence levels we used were "convincing", "probable", "possible", and "limited". We regarded recommendations for lifestyle changes as sufficiently sound only on the basis of convincing or probable evidence (2).

We did not conduct a systematic meta-analysis of comparable study data. Instead we adopted weighted hazard ratios (HR) from recently published meta-analyses (3, 4), in order to show effect sizes of individual factors. We used only HR and relative risk (RR) values after multivariate adjustment, in as far as this had been done in the publications we studied, since observational studies regarding diet/nutrition always have a complex association with people's general health behaviors. It is easy to imagine that a healthy diet is associated with a generally healthy lifestyle, so that studies that investigate the effects of healthy nutrition may attribute successes to this factor when in actual fact the entire lifestyle is responsible.

Results

Association of body weight and prognosis of breast cancer

Even earlier meta-analyses found that obese women have a higher risk for tumor recurrence and a higher mortality compared with slender people (5). Our own research into this topic identified 17 cohort studies (e1–e17). In 13 out of 15 studies with the end point all-cause mortality, a significant positive association between body mass index (BMI) and mortality was found; in one study a trend in this direction was identified *(eTable)*. Six out of 12 studies with the end point breast cancer specific mortality showed a significant positive association, three further studies showed a trend, and three studies (e3, e4, e13) did not find any association *(eTable)*.

Premenopausal overweight is associated with a lower risk for developing breast cancer, according to the WCRF data (2), whereas the present study found a positive association between BMI at the time of diagnosis and mortality not only in women with postmenopausal breast cancer but also in those with premenopausal breast cancer. Seven out of nine studies that differentiated between premenopausal and postmenopausal breast cancer showed significant positive associations, one study merely a trend, and one study no association (e4) *(eTable)*. This represents convincing evidence for an association between obesity and all-cause mortality and a probable evidence for an association between obesity and breast cancer specific mortality.

The results were less clear-cut for recurrence rates. Two (e6, e16) out of six studies with the end point breast cancer recurrence showed a significant association with BMI and two further studies (e10, e12) showed a trend; two further studies did not find any

association *(eTable)*. An unequivocal conclusion is therefore not possible.

Association of weight gain and breast cancer prognosis

The WCRF report stated that weight gain per se was a risk factor for developing postmenopausal breast cancer (2). Most observational studies found a weight gain in women after a breast cancer diagnosis. Seven cohort studies were identified to determine the importance of weight gain for breast cancer prognosis (e5, e8, e10, e14, e16, e18, e19). Five of six studies with the endpoint all-cause mortality and all four studies with the endpoint breast cancer specific mortality found a significant positive association with weight gain *(Table 1)*. No clear result was found for the end point recurrence rate. Only two of five studies showed a significant positive association with weight gain; three studies showed no association. The results provide convincing evidence of an increase in all-cause mortality and breast cancer specific mortality after weight gain subsequent to a breast cancer diagnosis.

The influence of diet/nutrition on the prognosis of breast cancer

Only very few cohort studies have thus far investigated the influence of diet/nutrition on the prognosis of breast cancer (6–9, e9, e11, e13, e20–e26). In 11 of these studies, the importance of the composition of macronutrients for mortality was analyzed as an end point.

Only one of three studies providing data about carbohydrate consumption (6, 7, e23) showed a protective effect for a high consumption. Of the six studies including data on fat intake, four showed a trend for a risk increase (7, e20, e21, e23) for a high consumption, only one showed a significantly increased risk (7). Three out of four cohort studies showed a protective effect for dietary fiber (6, 7, e21, e23), in two of these the results reached significance, yielding a pooled hazard ratio of 0.63 (3). A diet rich in fruit, vegetables, wholegrain products, legumes, fowl, and fish also showed a beneficial effect on all-cause mortality (e24, e26). By contrast, a typical Western diet with a high intake of bleached flour products, red meat, full-fat dairy products, etc, was found to be non-beneficial and was associated with an increase in non-breast cancer specific mortality (e24, e26) and a significant increase in all-cause mortality (e26).

Special food products, such as soy products or green tea—An evaluation of the Shanghai Breast Cancer Survival Study (SBCCS) found an inverse relation between the intake of soy products and the risk of recurrence (hazard ratio [HR] 0.68; 95% confidence interval [CI] 0.54 to 0.87, highest versus lowest quartile) and all-cause mortality (HR 0.71; CI 0.54 to 0.92) (8). A recent meta-analysis identified three further studies into the topic but did not find this inverse correlation (9).

Only a small number of observational studies and case-control studies have investigated the effect of green tea on breast cancer. A study from Japan, which

TABLE 1

Weight gain since breast cancer diagnosis and prognosis (recurrence rate, breast cancer specific mortality and all-cause mortality)

Author	No of cases, tumor stages	Mean follow-up (years)	End points	Menopausal status and/or age	Timing of data collection	Results
Camoriano JK et al., 1990 (e18)	646, LN positive	6.6	All-cause mortality, recurrence rate	pre-/post-menopausal	After diagnosis	Premenopausal women (n = 330): all-cause mortality: HR 1.62 (95% CI 1.01 to 2.62); p = 0.04; recurrence rate: HR 1.5; p = 0.17 Postmenopausal women (n = 215): all-cause mortality: n.s.*, recurrence rate: n.s.*
Kroenke CH et al., 2005 (e5)	5204, invasive, no metastases	9	Recurrence rate, breast cancer specific mortality, all-cause mortality	pre-/post-menopausal	After diagnosis	In never-smokers: recurrence rate: weight gain (n = 984, 156 cases) vs. stable weight (n = 677, 75 cases), p for trend = 0.01, breast cancer specific mortality: weight gain (n = 984, 123 deaths) vs. stable weight (n = 677, 48 deaths), p for trend = 0.03; all-cause mortality: weight gain (n = 984, 167 deaths) vs. stable weight (n = 677, 78 deaths), p for trend = 0.04; In former and current smokers: n.s.
Caan BJ et al., 2006 (e19)	3215, stages I to IIIa	6.1	Recurrence rate	18–70 years	After diagnosis	Moderate weight gain (5–10%) vs. stable weight: recurrence rate: HR 0.8 (95% CI 0.6 to 1.1), n.s. Notable weight gain (>10%) vs. stable weight recurrence rate: HR 0.9 (95% CI 0.7 to 1.2), n.s.
Cleveland RJ et al., 2007 (e8)	1508, invasive and in situ	5.6	Breast cancer specific mortality, all-cause mortality	pre-/post-menopausal, 25–98 years	Before diagnosis	Premenopausal: breast cancer specific mortality: weight gain >16 kg (n = 123, 19 deaths) vs. stable weight (n = 78, 6 deaths) HR 2.09 (95% CI 0.80 to 5.48), p for trend = 0.08 All-cause mortality: weight gain >16 kg (n = 123, 22 deaths) vs. stable weight (n = 78, 6 deaths) HR 2.45 (95% CI 0.96 to 6.27), p for trend = 0.062 Postmenopausal: breast cancer specific mortality: weight gain >12.7 kg (n = 162, 15 deaths) vs. stable weight (n = 370, 12 deaths) HR 2.95 (95% CI 1.36 to 6.43), n.s. All-cause mortality: weight gain >12.7 kg (n = 162, 38 deaths vs. stable weight (n = 370, 28 deaths) HR 2.69 (95% CI 1.63 to 4.43), n.s.
Caan BJ et al., 2008 (e10)	1692, stages I to IIIa	7	Recurrence rate, all-cause mortality	pre-/post-menopausal	After diagnosis	Recurrence rate: weight gain (n = 604, 65 events) vs. stable weight (n = 799, 100 events), p for trend 0.99 All-cause mortality: weight gain (n = 604, 52 deaths) vs. stable weight (n = 799, 100 deaths), p for trend 0.08
Nichols HB et al., 2009 (e14)	3993, invasive, no metastases	6.3	Breast cancer specific mortality, all-cause mortality	20–79 years	After diagnosis	Breast cancer specific mortality: per 5 kg weight gain (n = 2234, 77 deaths) vs. stable weight (n = 1037, 28 deaths), HR 1.13 (95% CI 1.03 to 1.25), p = 0.01 All-cause mortality: per 5 kg weight gain (n = 2234, 197 deaths) vs. stable weight (n = 1037, 98 deaths), HR 1.12 (95%.CI 1.04 to 1.22), p = 0.004
Chen X et al., 2010 (e16)	5042, all stages	3.8	Recurrence rate, breast cancer specific mortality, all-cause mortality	20–75 years	After diagnosis	Recurrence rate: weight gain ≥ 5 kg (n = 1060, 72 events) vs. stable weight (n = 866, 32 events), HR 1.90 (95% CI 1.23 to 2.93) Breast cancer specific mortality: weight gain ≥ 5 kg (n = 1060, 72 deaths) vs. stable weight (n = 866, 32 deaths), HR 1.90 (95% CI 1.23 to 2.93) All-cause mortality: weight gain ≥ 5 kg (n = 1096 , 69 deaths) vs. stable weight (n = 833, 35 deaths), HR 1.71 (95% CI 1.12 to 2.60)

LN, lymph node; HR, hazard ratio; RR, relative risk; n.s., non-significant; CI, confidence interval; * no exact data available

TABLE 2

Alcohol intake and breast cancer prognosis

Author	No of cases, tumor stages	Mean follow-up (years)	End points	Menopausal status and/or age	Timing of data collection	Results
Holmes MD et al., 1999 (6)	1982, invasive	18	All-cause mortality	pre-/post-menopausal	N/A	Highest vs. lowest quartile RR 0.92 (95% CI 0.66 to 1.27), n.s.
Borugian MJ et al., 2004 (e23)	603, all stages	10	Breast cancer specific mortality	pre-/post-menopausal	At diagnosis	Alcohol consumers vs. those not drinking alcohol, n.s.
Barnett GC et al., 2008 (e9)	4560, invasive	6.8	All-cause mortality	<55 years	After diagnosis	Risk per unit (= 8 g pure alcohol/week) (n = 4155, 564 deaths), HR 0.98 (95% CI 0.97 to 0.99), p = 0.0045
Reding KW et al., 2008 (e29)	1286, invasive	10 plus	All-cause mortality	≤ 45 years	Before diagnosis	Alcohol intake in the 5 years before diagnosis Consumer (n = 955, 254 deaths) vs non-consumer (n = 322, 106 deaths) HR 0.7 (95% CI 0.5 to 0.9)
Franceschi S et al., 2009 (e30)	1453, invasive	12.6	All-cause mortality	23–74 years	After diagnosis	Consumers of alcohol (n = 1127, 383 deaths) vs. never-drinkers (n = 326, 120 deaths), HR 0.98 (95% CI 0.79 to 1.22), n.s.
Flatt SW et al., 2010 (e31)	3088, stages I to IIIa	7.3	Recurrence rate, all-cause mortality	pre-/post-menopausal	After diagnosis	Moderate alcohol consumption (>300 mg/month) vs. alcohol <10 g/month Recurrence rate: drinker (n = 634, 100 events) vs. non-drinker (n = 1133, 213 events), HR 0,91 (95% CI 0.71 to 1.18)* All-cause mortality: drinker (n = 634, 52 deaths) vs. non-drinker (n = 1133, 139 deaths), HR 0.69 (95% CI 0.49 to 0.97)*

HR, hazard ratio; RR, relative risk; n. s., not significant; N/A, not available; 95 CII, 95% confidence interval; * no exact data available

included 472 patients with breast cancer of stages I–III reported a relative risk for tumor recurrence of 0.56 (CI 0.35 to 0.91), which was found only for women in tumor stages I–II who consumed five or more cups of green tea per day (10). Another cohort study (11) showed a similarly beneficial effect, which was seen upwards from three cups per day. Two formal meta-analyses concluded that the recurrence rate in women with breast cancer of stages I and II could be lowered on the basis of possible evidence (e27, e28). A recommendation for the consumption of green tea or isolated ingredients such as EGCG (epigallocatechin gallate) cannot be concluded from this.

Micronutrients and supplements—Some cohort studies investigated the influence of micronutrients on the prognosis of breast cancer. Individual evaluations have described beneficial effects for calcium (6), vitamin D (6, 12), vitamin B_2, folic acid (7), phosphorus (6), beta carotene, and vitamin C if ingested in food but not if taken as supplements (6, 7, 13, e20). The vast majority of these studies did not find any beneficial effects on the mortality of women with breast cancer for taking individual micronutrients or combinations thereof, such as calcium, folic acid, iron, selenium, zinc, niacin, beta carotene, vitamin A, vitamin C, or vitamin E (3).

Alcohol—Convincing evidence shows that regular consumption of alcohol increases the risk of breast cancer in premenopausal as well as postmenopausal women (2). Our evaluation of the six available cohort studies of women with diagnosed breast cancer presented a different, if not consistent, picture *(Table 2)*. For the end point all-cause mortality, three of the six studies (6, e19, e23, e29–e31) showed no association; three studies reported a drop in all-cause mortality, which is probably due to the known beneficial effect of moderate amounts of alcohol on cardiovascular mortality (e9, e29, e31).

Interventional studies—Two large lifestyle interventional studies in women with early stages of breast cancer have been conducted to date. Both were started in the early 1990s and captured hard end points such as disease-free survival (tumor recurrence, disease-specific mortality, and all-cause mortality). The Women's Intervention Nutrition Study (WINS) included 975 women who participated in telephone-based lifestyle advice, which aimed primarily to reduce fat intake to less than 15% of the total daily energy intake (14). The therapeutic goal of the Women's Healthy Eating and Living Study (WHEL) was a reduction in fat intake to 15% to 20% of total energy intake and an increase in the intake of fruits, vegetables, and other foods that are rich in dietary fiber (15).

Neither study found an effect of the intervention on mortality (WINS: HR 0.89; p = 0.56; WHEL: HR 0.97, p = 0.82). The primary end point—recurrence-free survival—was only just missed in the WIN study (HR 0.76, p = 0.077), and clearly missed in the WHEL study (HR 0.99, p = 0.87). A later evaluation of the WHEL study did, however, find a significant interventional effect in women with the best diet (the highest intake of fruits, vegetables, dietary fiber, and lowest amount of fat) (e32).

Discussion

The incidence of breast cancer is increasing in Germany in the same way as in the rest of the world. In view of this increase, new concepts and strategies are desirable to prevent tumor recurrence and improve the quality of life and survival expectancy in those affected. The study results we presented imply that lifestyle choices can modify the prognosis for these patients, but our understanding of these associations is limited and incomplete.

What is currently known is derived almost entirely from cohort studies. Although the cohort sizes have notably increased in recent years and the quality of data collection has improved, intrinsic methodological limitations remain that restrict the validity of the results thus gained. Cohort studies can merely highlight associations; they cannot provide any information on cause and effect. Owing to the multitude of interactions between known and unknown factors—especially in the context of lifestyle—biases and incidental findings cannot be excluded. The result: reliable conclusions are possible only for effects that consistently occur in different cohorts or that have been confirmed in interventional studies.

According to the WCRF's assessment criteria, the present analysis provides convincing evidence that a high BMI is associated with a worse prognosis for women with breast cancer. This association has a high biological plausibility, as has been shown repeatedly in the recent past (16, 17). A new meta-analysis found an increase in all-cause mortality and breast cancer specific mortality in association with obesity of 30%, respectively, which was more pronounced in premenopausal women than in postmenopausal women (4).

Weight gain after a diagnosis of breast cancer is common (18, 19). The reasons are complex and poorly understood (5, 18, 20, e33, e34). Such weight gain obviously increases the mortality risk, so that this aspect should be subject to great attention in the future.

A result in the present analysis that is particularly worth mentioning is the absence of evidence for the benefit of many products that women with breast cancer are often offered as support measures. This is particularly the case for the multitude of vitamin and mineral preparations on offer. According to a recent US study, more than 60% of women receiving adjuvant therapy for breast cancer take preparations containing beta carotene, vitamin C, vitamin E, or selenium (e35). For individual substances—for example, antioxidant preparations—if taken while undergoing chemotherapy or radiotherapy, a certain risk increase cannot be excluded (21).

An interesting finding of our literature search was the fact that the analysis of the prognostic factors for breast cancer deviates partly from the results reported by the WCFR (2). The WCRF reported convincing evidence for alcohol in the sense of a risk increase for

premenopausal and postmenopausal breast cancer, whereas our evaluation did not find a negative influence, however, this is probably masked by the beneficial effects of moderate alcohol consumption on cardiovascular risk. A convincing explanation for this discrepancy is so far lacking.

The two interventional studies in women with breast cancer that have been conducted so far (14, 15) addressed the question of the degree to which reducing fat intake to below 15% to 20% of the total energy intake improves the prognosis. The intervention programs did, however, not consider the quality of the fat and left body weight and exercise activity altogether out of the analysis. Since the desired fat reduction was only partly successful and had little effect on prognosis, the question is how future lifestyle intervention programs for women with breast cancer should be designed. Subgroup analyses of both studies showed that if the instructions were adhered to then a positive influence on individual end variables was noted (e32). However, nowadays the consensus is mostly that the focus is on weight management and exercise and that multimodal approaches should be studied (22).

On this background, new interventional studies are urgently needed. In view of the good prognosis for women with non-metastatic breast cancer (1), other intervention objectives should also be considered, such as the reduction of cardiovascular disorders that is to be expected from life style adjustment, as well as type 2 diabetes or the women's quality of life. Lifestyle programs should not be limited only to preventing tumor recurrence, as their benefits can be assumed to be rather more comprehensive. In Germany, the SUCCESS-C Study is currently investigating the benefit of a two-year lifestyle intervention with moderate weight reduction on the recurrence-free survival of women with non-metastatic breast cancer (23).

KEY MESSAGES

- Overweight/obesity is associated with increased mortality in women with premenopausal and postmenopausal breast cancer.

- The widespread and common weight gain after a breast cancer diagnosis is also indicative of a poor prognosis.

- A healthy diet with a high proportion of fruit, vegetables, wholegrain products, and low amounts of fat seems to be associated with better survival. However, interventional studies have thus far not confirmed this association. The typical Western diet is associated with a poorer prognosis.

- There is no indication that supplementation with vitamins, minerals, or trace elements improves the prognosis of women with breast cancer.

- Although the importance of alcohol is still not clear, only very moderate consumptions seems acceptable.

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eTABLE

Body mass index (BMI) at breast cancer diagnosis and prognosis (recurrence rate, breast cancer specific mortality and all-cause mortality)

Author	No of cases, tumor stages	Mean follow-up	End points	Menopausal status and/or age	Timing of BMI measurement	Results
Daling JR et al., 2001 (e1)	1177, invasive, ductal	Not specified	All-cause mortality after 5 and 10 years	<47 years	At diagnosis	All-cause mortality after 10 years: BMI highest quartile (n = 132, 44 deaths) vs. lowest quartile (n = 125, 27 deaths) HR 1.7 (95% CI 1.0 to 2.9); p<0.05
Dignam et al., 2003 (e2)	3385, ER positive, early stages	13.8	Recurrence rate, breast cancer specific mortality, all-cause mortality	pre-/postmenopausal	After diagnosis	Recurrence rate (787 events in total): BMI ≥ 30 kg/m² vs. BMI <25 kg/m²; HR 0.98 (95% CI 0.80 to 1.18); n.s. Breast cancer specific mortality (595 deaths): BMI ≥ 30 vs. BMI<25 kg/m²; n.s. All-cause mortality (983 deaths): BMI ≥ 30 vs. BMI<25; HR 1.31 (95% CI 1.12 to 1.54); p<0.001
Berclaz G et al., 2004 (e3)	6792, early stages	14	Breast cancer-free survival, total survival	pre-/postmenopausal	After diagnosis	Breast cancer-free survival: BMI ≥ 30 kg/m² vs. BMI < 25 kg/m², n.s. 10-year cancer-free survival: obese women (n = 1 024) 42 ± 2% "intermediate" women (n = 2038) 44 ± 1% women of normal weight (n = 3308) 45 ± 1 % Total survival: BMI ≥ 30 kg/m² vs. BMI <25 kg/m², p = 0.03 10-year total survival: obese women (n = 1024) 55 ± 2% "intermediate" women (n = 2038): 57 ± 1% women of normal weight (n = 3308) 61 ± 1%
Enger SM et al., 2004 (e4)	717, all stages	10.4	Breast cancer specific mortality	premenopausal ≤ 40 years	Before diagnosis	Breast cancer specific mortality: highest BMI quartile (n = 118, 64 deaths) vs. lowest quartile (n = 110, 65 deaths), n.s.
Kroenke CH et al., 2005 (e5)	5204, invasive, no metastases	9	Recurrence rate, breast cancer specific mortality, all-cause mortality	pre-/postmenopausal	Before diagnosis	Recurrent tumors (n = 714): RR 1.00 (95% CI 0.76 to 1.31); n.s. Breast cancer specific mortality (n = 533): RR 1.09 (95% CI 0.80 to 1.48); p for trend = 0.045 All-cause mortality (n = 860): RR 1.20 (95% CI 0.95 to 1.52); p for trend <0.001 Associations with BMI stronger in premenopausal than in postmenopausal women
Loi S et al., 2005 (e6)	1360, no metastases	5	Recurrence rate, all-cause mortality	<60 years at diagnosis 74% premenopausal	Before diagnosis	Recurrence rate (not reported): obese vs. normal weight: HR 1.57 (95% CI 1.11 to 2.22); p= 0.02 All-cause mortality (184 deaths): obese vs. normal weight: HR 1.56 (95% CI 1.01 to 2.40); p= 0.05 Premenopausal women: Recurrence rate (not reported): obese vs. normal weight: HR 1.50 (95% CI 1.00 to 2.26), p = 0.06 All-cause mortality: obese vs. normal weight: HR 1.71 (95% CI 1.05 to 2.77), p = 0.04
Whiteman MK et al., 2005 (e7)	3924, all stages	14.6	Breast cancer specific mortality	20–54 years	Before diagnosis	Breast cancer specific mortality: BMI ≥ 30 (n = 263, 109 deaths) vs. BMI ≤ 22.99 (n = 2331, 733 deaths); HR 1.34 (95% CI 1.09 to 1.65); p for trend 0.0001 Premenopausal women: Breast cancer specific mortality: BMI ≥ 30 (n = 161, 65 deaths) vs. BMI ≤ 22.99 (n = 1576, 501 deaths), HR 1.38 (95% CI 1.05 to 1.80), p for trend = 0.002
Cleveland RJ et al., 2007 (e8)	1508, invasive and in situ	5.5	Breast cancer specific mortality, all-cause mortality	pre-/postmenopausal	Before diagnosis	Breast cancer specific mortality (n = 127): obese vs. normal weight: HR 2.85 (95% CI 1.30 to 6.24) All-cause mortality (n = 196): HR 2.62 (95% CI 1.26 to 5.45)

Barnett GC et al., 2008 (e9)	4560, invasive	6.8	All-cause mortality	<55 years	After diagnosis	All-cause mortality (620 deaths): Increase per BMI unit; p = 0.00094
Caan et al., 2008 (e10)	1692, stages I to IIIa	7	Recurrence rate, breast cancer specific mortality, all-cause mortality	pre-/postmeno-pausal (58.3 years at diagnosis)	1 year before diagnosis	Recurrence rate (207 events): HR 1.3 (95% CI 0.7 to 1.4); n.s. Breast cancer specific mortality (90 deaths): HR 1.6 (95% CI 0.9 to 2.7); n.s. All-cause mortality (n = 160 deaths): HR 1.6 (95% CI 1.1 to 2.3); p = 0,03
Dal Maso L et al., 2008 (e11)	1453, invasive	12.6	Breast cancer specific mortality, all-cause mortality	pre-/postmeno-pausal	After diagnosis	Breast cancer specific mortality (398 deaths): HR 1.38 (95% CI 1.02 to 1.86); p for trend 0.06 All-cause mortality (503 deaths): HR 1.29 (95% CI 0.99 to 1.68); p for trend = 0.12
Majed B et al., 2008 (e12)	14 709, all stages	8	Recurrence rate, disease-free survival, total survival	pre-/postmeno-pausal	At diagnosis	Recurrence rate: HR 1.12 (95% CI 1.00 to 1.26); n.s. Disease-free survival (n = 4876): HR 1.10 (95% CI 0.99 to 1.22) Total survival (n = 3693): HR 1.12 (95% CI 0.99 to 1.25); p = 0.06
Emaus A et al., 2009 (e13)	1364, all stages	8.2	All-cause mortality	27–79 years	Before diagnosis	All-cause mortality (429 deaths): p for trend = 0.04 for all BMI categories BMI ≥ 30 (n = 147, 60 deaths) vs. BMI 18.5 to 25 kg/m² (n = 808, 232 deaths) HR 1.47 (95% CI 1.08 to 1.99)
Nichols HB et al., 2009 (e14)	3993, invasive, no metastases	6.3	Breast cancer specific mortality, all-cause mortality	20–79 years	Before and after diagnosis	Breast cancer specific mortality: BMI ≥ 30 kg/m² (n = 2058, 50 deaths) vs. BMI 18.5 to 25 kg/m² (n = 1479, 31 deaths) Before diagnosis (n = 639, 24 deaths); n.s. After diagnosis (n = 977, 48 deaths) HR 2.28 (95% CI 1.43 to 3.64) All-cause mortality: BMI ≥ 30 kg/m² (n = 2058, 178 deaths) vs. BMI 18.5 to 25 kg/m² (n = 1479, 140 deaths) Before diagnosis (n = 639, 93 deaths) HR 1.52 (95% CI 1.17 to 1.98) After diagnosis (n = 977, 122 deaths) HR 1.27 (95% CI 0.99 to 1.64)
West-Wright CN et al., 2009 (e15)	3539, invasive	At least 1 year	Breast cancer specific mortality, all-cause mortality	pre-/postmeno-pausal	After diagnosis	Breast cancer specific mortality: BMI ≥ 30 (n = 469, 39 deaths) vs. BMI <25 kg/m² (n = 1945, 99 deaths); RR 1.71 (95% CI 1.16 to 2.53) All-cause mortality: BMI ≥ 30 (n = 469, 72 deaths) vs. BMI <25 kg/m² (n = 1945, 220 deaths); RR 1.42 (95% CI 1.08 to 1.88)
Chen X et al., 2010 (e16)	5042, all stages	3..8	Recurrence rate, breast cancer specific mortality, all-cause mortality	20–75 years	Before, at, and after diagnosis	At diagnosis: Recurrences/breast cancer specific mortality: BMI ≥ 30 kg/m² (n = 250, 41 deaths) vs. BMI 18.5 to 24.9 kg/m² (n = 3213, 284 deaths); HR 1.44 (95% CI 1.02 to 2.03) All-cause mortality: BMI ≥ 30 kg/m² (n = 256, 44 deaths) vs. BMI 18.5 to 24.9 kg/m² (n = 3238, 258 deaths); HR 1.55 (95% CI 1.10 to 2.17) Similar results for premenopausal and post-menopausal women
Keegan TH et al., 2010 (e17)	4153, invasive	7.8	All-cause mortality	<65 years	Before diagnosis	All-cause mortality: obese women (n = 712) vs. women of normal weight (n = 2220); HR 1.21 (95% CI 1.00 to 1.48); p for hetero-geneity = 0.03 BMI and all-cause mortality p for trend = 0.01 for women ≥ 50 years (n = 1699)

ER, estrogen receptor; HR, hazard ratio; RR, relative risk; n.s., non-significant; CI, confidence interval; * no exact data available