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To cite this version:

Eliane Kellen, Greet Vansant, Marie-Rose Christiaens, Patrick Neven, Erik Limbergen. Lifestyle changes and breast cancer prognosis: a review. Breast Cancer Research and Treatment, 2008, 114 (1), pp.13-22. 10.1007/s10549-008-9990-8 . hal-00478334

HAL Id: hal-00478334

https://hal.science/hal-00478334

Submitted on 30 Apr 2010

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Breast Cancer Res Treat (2009) 114:13–22
DOI 10.1007/s10549-008-9990-8

REVIEW

Lifestyle changes and breast cancer prognosis: a review

Eliane Kellen · Greet Vansant · Marie-Rose Christiaens · Patrick Neven · Erik Van Limbergen

Received: 21 March 2008 / Accepted: 21 March 2008 / Published online: 4 April 2008
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Abstract *Objective* Because of its high incidence and improving survival, breast cancer is currently the most prevalent cancer in the world. We reviewed the published literature in our search for modifiable factors valuable as an adjuvant health measure to surgery, radio and systemic therapy for breast cancer. *Methods* We included material which was identified from computerised searches of PubMed (1966 to May, 2007). Published material was restricted to prospective cohort studies and randomised clinical trials. We reviewed the literature concerning the association between physical activity, smoking, weight gain after the diagnosis, diet and prognosis. *Results and conclusion* We conclude that life style changes following standard breast cancer therapy are highly recommended (although scientific evidence is still lacking for some of inconsistency regarding available data). They include physical activity, weight control, high consumption of fruit and vegetables, and a reduction of dietary fat intake.

Keywords Breast cancer · Life style · Prognosis

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Introduction

Breast cancer is by far the most frequent cancer of women. More than half of the cases occur in industrialized countries. Although, the incidence is more modest in Eastern Europe, South America, Southern Africa, and Western Asia, it is still the most common female cancer in these geographic regions. The rates are low in most parts of Africa (with the exception of South Africa) and in most of Asia [1].

Most of the breast cancer risk factors described in the literature are related to a woman's life time exposure to oestrogens: early menarche and late menopause, high total numbers of menstrual cycles and use of oestro-progestons increase the risk; while it is reduced by an early first birth and early menopause [2]. Lactation protects against breast cancer while alcohol increases the risk. The relationship of body fatness with breast cancer risk is equivocal. It probable decreases the risk of premenopause cancer while it increases the risk for postmenopause cancer. Postmenopausal breast cancer seems to be positively associated with abdominal fatness and adult weight gain and negatively with physical activity [3]. Data regarding the role of soy remains conflicting, but adolescent exposure appears to be protective [4]. Positive or negative effects of dietary exposures may be limited to subgroups of women defined by specific genetic characteristics [5]. Breast cancer risk is positively associated with increased smoking during the period between menarche and first childbirth, suggesting that the sensitivity of the female breast to tobacco carcinogens is increased during adolescence and early adulthood [6].

The large variability in the clinical outcome of women with morphological identical breast cancers receiving comparable therapeutic strategies suggest the importance of other life style changes. We therefore reviewed the

available published literature in our search for modifiable life style factors that may be useful as adjuvant treatment to surgery, radio and systemic therapy for breast cancer.

Search strategy and selection criteria

Material included in this review was identified from computerised searches of PubMed (1966 to February, 2008) using the medical subject headings (MeSH) terms "breast neoplasm " OR "breast cancer", "AND prognosis" "AND survival" "AND diet" "AND life style" "AND physical activity" "AND smoking" "AND obesity" "AND phytoestrogenes" "AND dietary fat". Only peer-reviewed English language papers were eligible for inclusion. Additional information and studies were obtained by checking the reference lists from retrieved papers. Only prospective breast cancer cohort studies and randomised clinical trials reporting on breast cancer recurrence and survival were included. Currently, few such studies have been designed with the objective to investigate the association between different lifestyle factors and breast cancer prognosis. Most epidemiologic studies were designed to examine aetiology and do therefore not answer whether or not the studied population continued their original lifestyle or altered it after the diagnosis of breast cancer which may bias the results (Table 1).

The Life After Cancer Epidemiology (LACE) Study consists of cohort of 2,321 early stage breast cancer survivors and was designed to investigate how modifiable behavioral risk factors such as diet and physical activity affect quality of life and long-term survival [7].

The Health, Eating, Activity, and Lifestyle (HEAL) Study is a population-based, multicenter prospective cohort study that has enrolled 1,185 breast cancer patients to study the influence of factors such as body weight, physical activity and diet on prognosis [8].

The Shanghai Breast Cancer Survival (SBSS) Study comprises 2,236 Chinese women with breast cancer and collects information on lifestyle related factors and disease- and treatment related factors [9].

The Women's Healthy Eating and Living (WHEL) Study is a multisite randomized controlled trial of the effectiveness of a high-vegetable, low-fat diet, in reducing additional breast cancer events and early death in women with early-stage invasive breast cancer (within 4 years of diagnosis). The study randomly assigned 3,088 women to an intensive diet intervention or to a comparison group [10].

The Women's Intervention Nutrition (WINS) Study, a randomized, prospective clinical trial of 2,437 assigned women with resected, early-stage breast cancer, receiving conventional therapy, to a dietary intervention group receiving a program of individualized instruction for reducing total fat intake or a dietary control group with minimal dietary counselling. The dietary intervention aims to reduce the percentage of calories with 15% of habitual intake while maintaining nutritional adequacy [11].

Table 1 Overview of the prospective studies and randomized clinical studies investing the association between life style factors and breast cancer prognosis

	Country	Breast cancer	Major exposures of interest
Prospective cohort studies			
Life After Cancer Epidemiology (LACE) Study [7]	US	Stage I & II invasive	Diet Physical activity Quality of life
Health, Eating, and Lifestyle (HEAL) Study [8]	US	In situ breast carcinoma to stage IIIa breast carcinoma	Diet Physical activity Weight
Shanghai Breast Cancer Survival (SBSS) Study [9]	China	Newly diagnosed	Life-style Disease- and treatment-related factors Quality of life
Randomized clinical trials			
Women's Healthy Eating and Living (WHEL) Study [10]	US	Stage I (≥1 cm), II or IIIA invasive	High-vegetable, low-fat diet
Women's Intervention Nutrition (WINS) Study [11]	US	Invasive (exclusion for tumour size less than 1 cm with negative nodes; tumour size greater than 5 cm with positive nodes; 10 or more nodes positive)	Dietary fat reduction

Results

Physical activity

A cohort study of 2,987 women in the Nurses' Health Study, diagnosed with stage I, II or III breast cancer found a protective effect of physical activity on cancer-related mortality. The greatest benefit occurred in women who performed the equivalent of walking 3–5 h per week at an average pace and among women with hormone-responsive tumours [12]. Similar results were found by a cohort study of 4,482 invasive breast cancer patients [13] and for two studies that investigated the relationship between breast cancer mortality and pre-diagnostic physical activity [14, 15]. Results from the WHEL study indicated that the combination of consuming at least five servings of vegetables-fruits and physical activity (30 min of walking at moderate pace for 6 days a week) is associated with an increase in survival in women with estrogen-positive receptor tumours [16]. However, an Australian cohort of 451 women with breast cancer found no association. Likewise a cohort study in Canada of 603 women with incident breast cancer found no association between physical activity and breast cancer mortality [17].

A trial that randomized sedentary, obese breast cancer patients to a cardiovascular and strength training exercise intervention or to a usual care control demonstrated that exercise is associated with a decrease in insulin levels [18].

Biological mechanism

The literature remains controversial whether or not in post-menopausal women, increased physical activity is associated with decreased serum concentrations of oestradiol and oestrone [19]. Nonetheless, a randomized clinical trial found that exercise may decrease serum oestrogens levels in previously sedentary, obese postmenopausal women [20].

In premenopausal women, research indicates longer menstrual cycles, and lower progesterone and oestradiol levels in athletes compared with control subjects. A randomized controlled trial concluded that a 12-week aerobic exercise training intervention did not alter oestrogen metabolism in premenopausal women [21].

High circulating levels of Insulin-Like Growth factor (IGF)-1 may be positively associated with increased risk of breast cancer. The current literature is not conclusive on the relation between increasing physical activity and IGF-1 levels [19]. However, it was demonstrated that IGF-1 is a mediator of estradiol mitogenic effects [22].

Smoking

A cohort study of 5,056 women in the Nurses' Health Study, diagnosed with breast cancer, found no association between a history of smoking and breast cancer-related mortality or an increased risk of breast cancer recurrence [23]. Similar results were concluded by two other cohort studies [24, 25]. In contrast, a Swedish cohort study concluded that the breast cancer mortality was the lowest in those who had never smoked, the highest in smokers, and somewhere in between in ex-smokers [26].

Biological mechanism

Nicotine is the main immunosuppressive constituent of cigarette smoke, which inhibits both the innate and adaptive immune responses [27]. Smoking may have an 'anti-oestrogenic' effect although endogenous oestrogen levels have not been found to differ significantly when comparing current smokers with former smokers or non-smokers [28]. However, it should be noted that cigarette smoking is inversely associated with the risk of endometrial cancer among postmenopausal women, which is another oestrogen dependent tumour [29].

Obesity and weight gain after the diagnosis

The majority of the existing literature indicates a negative relationship between obesity and poor prognosis of breast cancer in both pre- and post-menopausal women [30]. Weight gain after diagnosis has been reported frequently, possibly through increased caloric intake, changes in physical activity and change in host metabolic status [31]. Women who gained weight after diagnosis are found to be at greater risk for breast cancer recurrence and death compared to women with a lower body mass index (BMI) [32].

Analyses from the Nurses' Health Study showed that weight and weight gain after the date of diagnosis were related to higher rates of breast cancer recurrence and mortality. These findings were especially apparent in women who never smoked, among women with earlier stage disease or those who were normal weight before diagnosis [33]. In contrast, a collaborative effort between the LACE study and the WHEL study, did not observe an association between post-diagnosis weight gain and recurrence risk in the first 5–7 years post-diagnosis [34].

If circulating estrogen levels are the linking mechanism between adiposity and breast cancer recurrence, weight loss may no longer have an impact on recurrence or survival in postmenopausal women with estrogen-positve receptors treated with the third generation aromitase inhibitors (exemestane, anastrozole, letrozole). As these drugs suppress estradiol levels in post-menopausal women by 84% or more [35].

Biological mechanism

Increasing BMI is associated with increased oestradiol levels. Hyperinsulinism has been associated with a poor breast cancer prognosis, possibly mediated by the neuroendocrine hormone leptin that is produced by adipose tissue [28]. Obese postmenopausal breast cancer survivors have increased estrone, estradiol, free estradiol, levels and decreased sex-hormone-binding globulin levels [36]. Furthermore, it has been suggested that obese women with breast cancer may receive reduced doses of adjuvant chemotherapy [37]. Higher BMI has been related to more advanced stages of breast cancer at diagnosis in terms of tumour size [38]. Obesity appears not to interfere with the efficacy of tamoxifen in women with lymph-node negative, oestrogen receptor-positive breast cancer [39].

Phytoestrogenes

Phytooestrogens are plant compounds that are structurally similar to mammalian oestrogens. They possess oestrogenic and antioestrogenic properties through binding on oestrogen receptors. Some data from in vitro and animal studies suggest that isoflavones, especially genistein, may stimulate the growth of oestrogen-sensitive tumours. Further research is therefore needed to determine effect of soy foods or isoflavones on breast cancer risk in high-risk women and on the survival of breast cancer patients [40]. Although, a Chinese study found no relationship between soy food intake before diagnosis and survival [41], it is not recommended to use soy to reduce menopausal symptoms in breast cancer patients [4].

It has been suggested that phytooestrogenes may influence the effect of tamoxifen, a selective oestrogen receptor modulator, in breast cancer treatment either in a antagonistic or synergistic way [4, 42]. However, a cross-sectional study in Asian Americans with breast cancer who were tamoxifen users found no relation between self-reported intake of soy and serum levels of isoflavones [43].

It should be noted that estrogen therapy is contraindicated after the diagnosis of breast cancer [44, 45].

Dietary fat

In women with oestrogen receptor positive breast cancer, a positive association between treatment failure and high intakes of total fat, saturated fat and polyunsaturated fatty acid has been suggested [46]. The association between dietary fat intake and reduced survival has been confirmed in both postmenopausal and premenopausal breast cancer patients [47–51]. Interim results of the WINS study suggest a benefit of dietary fat reduction on relapse-free survival. Secondary analyses suggested a stronger effect for dietary fat reduction on breast cancer recurrence in women with hormone receptor—negative cancers compared with women whose cancers were hormone receptor positive [52]. In contrast, the Nurses' Health Study did not conclude that a low fat diet after diagnosis leads to a survival advantage [53]. The same conclusion was reached by a prospective study of 213 breast cancer patients in Japan; it should be remarked that Japanese women develop breast cancer at an earlier age and consume relatively small amounts of fat (mean dietary fat intake was about 23% of calories) [54].

Biological mechanism

Experimental studies indicate that the polyunsaturated fatty acids, rich in linoleic acid enhance the promotion and progression of mammary cancer, whereas omega-3 fatty acid-containing fish exert a protective effect [55]. Laboratory and animal experimental evidence indicate that dietary fat intake influences breast cancer growth through changes in circulatory hormonal levels, changes in cell membrane structure and function, changes in prostaglandin and cytokine/monokine levels and altered regulatory gene expression [31]. A high-fiber, low fat diet intervention has been shown to be associated with reduced serum bioavaliable oestradiol concentration in women diagnosed with breast cancer [56].

Other dietary macro- and micronutrients

It has been shown that in post-menopausal women diagnosed with breast cancer, reduced fat and increased fiber, vegetable and fruit intakes improves overall survival [48]. But analyses from the Nurses' Health Study found that adherence to a prudent dietary pattern (characterized by a diet high in fruits, vegetables, whole grains, legumes, poultry and fish) was not associated with breast-cancer mortality but was negatively related to mortality from other causes [57]. The WHEL randomized trial confirmed that adherence to a diet very high in vegetables, fruit and fiber and low in fat does not reduce breast cancer recurrence or mortality [58]. In contrast, high consumption of β-carotene and vitamin C seems to influence survival [59]. Supplement use of vitamin C or E has been suggested to be associated with an decrease in breast cancer recurrence or breast-cancer related death [60]. Women, assigned to the non-intervention group of the WHEL study, with high plasma-carotenoid concentration, had a significantly reduced risk for breast cancer recurrence [61]. Interestingly, analyses of a cohort study of 477 breast cancer patients found that the association between key dietary variables with survival may be U-shaped and not linear. Thus moderate, rather than low, fat intakes are associated

with optimal survival [62]. A randomized clinical trial of fenretinide (a synthetic retinoid) showed a reduction of second breast cancer, which was more apparent among premenopausal women [63].

No evidence has been found that antioxidant vitamin supplements reduce the toxicity associated with chemotherapy [64]. Some authors even advise against the use of antioxidant supplements during chemotherapy or radiotherapy [65].

High alcohol consumption may be associated with an increase in breast cancer mortality [66].

Biological mechanism

The cancer-preventive capacities of carotenoids are attributed to their anti-oxidant capacities and their effect on gap junctional communication which play a role in the regulation of cell growth, differentiation and apoptosis [67]. It has been demonstrated that carotenoids influence the proliferative capacity and differentiation of mammary epithelial cells [68]. But the negative relationship between prognosis and increased fruit and vegetable consumption may partly due to the fact that a high fruit and vegetable consumption is merely a marker for low dietary fat intake. An increased estrogen concentration and a change in folate metabolism are mentioned among the mechanisms linking alcohol with breast cancer [69].

Discussion

Despite the wealth of etiologic studies on breast cancer risk and the growing number of breast cancer survivors, surprising little is known on the association between life style changes made after the diagnosis of breast cancer and the outcome. Currently, only two randomized control trials are studying the relationship between lifestyle related factors and prognosis [10, 11]. Both of them restricted inclusion to early stage breast cancer. While merely three large cohort studies of breast cancer patients are collecting data [7–9].

Based on available literature, a multidisciplinary approach regarding breast cancer is recommended and should include physical activity, body weight control, high consumption of fruit and vegetables, and a reduction of dietary fat intake. Recent results from the WHEL study suggested that a healthy lifestyle that combines high levels of fruit and vegetables consumption with physical activity is associated with an increase in survival [16]. Thus rather than one factor, a combination of lifestyle behaviors may improve breast cancer survival [70]. Besides the beneficial effect on recurrence, a healthy diet and regular exercise has the potential to reduce the risk of co morbidity (such as other cancers, cardiovascular disease, diabetes, etc.) and improving the quality of life (through a reduction of the risk on fatigue and depression) [71]. The American Cancer Society has summarized the best clinical practices related to optimal nutrition and physical activity during treatment and recovery, living after recovery from treatment and living with advanced cancer [72]. An overview of other resources available concerning information and health promotion to cancer survivors is given elsewhere [71]. Although many patients with cancer report healthier lifestyles after diagnosis, these changes might be temporary. Few studies have investigated the most appropriate intervention time (at diagnosis or later), patients' preferences about delivery of interventions or the relative efficacy of different methods (clinic versus home-based, face-to-face counselling, mailed interventions, telephone counselling, etc.) [71]. The FRESH START trial which included newly diagnosed breast or prostate cancer patients found that tailored mailed interventions are more effective in promoting healthful life styles (which included exercise, consumption of fruit and vegetables, overall diet quality, and decreasing intake of fat and saturated fat) than standardized materials [73]. More research is warranted. Unfortunately, although cancer survivors may be susceptible to health promotion, many health care providers may miss opportunities to counsel survivors about healthy behaviours [74]. Nevertheless, health care providers do have an important educational role concerning modifiable causes of cancer. A survey of cancer survivors' beliefs showed that the respondents underestimated the importance of behavioral factors (such as obesity and physical inactivity) known to be related to be with increased cancer risk, while overestimating the importance of stress and environmental pollution [75].

More research is needed before conclusive advice can be given to women with breast cancer. Intervention studies should answer on what lifestyle changes may be used as adjuvant therapy or as a modifier of tumor growth and progression. Future studies on the association between breast cancer prognosis and modifiable factors need to obtain complete clinical, dietary, and lifestyle information at moment of breast cancer diagnosis and this should be updated regularly during follow up. Albeit a challenge in designing, clinical trials are needed to determine the effect of physical activity on the recurrence and mortality of breast cancer [76]. To date, the WINS study is the first randomized trial that suggested that a dietary intervention may reduce breast cancer recurrence [52]. Future studies should investigate whether or not there is a threshold of dietary fat intake at which an increase in tumour recurrence is observed (Table 2).

Table 2 Overview of the different studies that investigated the relationship between lifestyle changes and breast cancer prognosis

Author, year (reference)	No. of cases	Median length followed	Outcome	Relative risk/hazard ratio (95% CI) comparison of highest quartile/quintile vs lowest	Adjustment confounding variables
Physical activity					
Holmes et al. (2005) [12]	2,987	8 years	Breast cancer mortality	**RR: 0.60 (0.40–0.89)**	Age, interval between diagnosis and physical activity assessment, smoking, BMI, menopausal status and hormone therapy use, age at first birth and parity, oral contraceptive use, energy intake, energy-adjusted protein intake, disease stage, radiation treatment, chemotherapy and tamoxifen treatment.
			Recurrence	RR: 0.74 (0.53–1.04)	
Holick et al. (2008) [13]	4,482	5.6 years	Breast cancer mortality	**HR: 0.51 (0.29–0.89)**	Age at diagnosis, stage at diagnosis, state of residence, interval between diagnosis and physical assessment, post diagnosis BMI, post diagnosis menopausal status, post diagnosis hormone therapy use, total energy intake year before enrolment, education level, family history of breast cancer at diagnosis, and initial treatment modality.
Abrahamson et al. (2006) [14]	1,264	8–10 years	Overall mortality	HR: 0.78 (0.56–1.08)	Stage and income.
Enger et al. (2004) [15]	717	10.4 years	Breast cancer mortality	HR: 0.78 (0.45–1.34)	Age, stage at diagnosis and BMI.
Borugian et al. (2004) [17]	603	Between 7.9 (Stage II) and 8.3 years (Stage I)	Breast cancer mortality	RR: 1.0 (0.6–1.6)	Age, total caloric intake, stage at diagnosis.
In combination with diet rich in fruit/vegetables					
Pierce et al. (2007) [16]	1,490	6.7 years	Mortality	**HR: 0.56 (0.31–0.98)**	Age, alcohol, tumour hormone receptor status and time from diagnosis to study entry.
Smoking (current versus never smoker)					
Holmes et al. (2007) [23]	5,056	8.25 years	Breast cancer mortality	RR: 1.02 (0.83–1.24)	Age, alcohol intake, energy, protein, vitamin C and β carotene intake, estrogen receptor, progesterone receptor, body mass index, oral contraceptive use, stage, tumour type, categories of treatment, year of diagnosis, age at first birth and parity, menopausal status and postmenopausal hormone use.
			Recurrence	RR: 1.07(0.88–1.29)	
Fentiman et al. (2005) [24]	166	11 years	Breast cancer survival	HR: 1.08 (0.55–2.13)	Stage, tumour grade, tumour size, age at diagnosis and menopausal status.
			Distant relapse-free survival	HR: 1.39 (0.72–2.68)	
Sagiv et al. (2007) [25]	1,273	5.8 years	Breast cancer mortality	HR: 1.04 (0.63–1.71)	Age at diagnosis, household income, hormone-replacement therapy, and length of residence in interview home.
Manjer et al. (2000) [26]	792	12.1 years	Breast cancer mortality	**RR: 2.14 (1.47–3.10)**	Age, stage at diagnosis.
Obesity and weight gain after diagnosis					

Table 2 continued

Author, year (reference)	No. of cases	Median length followed	Outcome	Relative risk/hazard ratio (95% CI) comparison of highest quartile/quintile vs lowest	Adjustment confounding variables
Kroenke et al. (2005) [33]	5,204	9 years	Breast cancer mortality	RR: 1.09 (0.80–1.48)	Age, oral contraceptive use , birth index, menopausal status, age at menopause, use of hormone replacement therapy, smoking status, protein intake, tumour size, nodal status, chemotherapy, and tamoxifen.
			Recurrence	Subgroup never smokers: **RR: 1.83 (1.09–3.05)**	
				Subgroup premenopausal: **RR: 1.20 (1.13–3.61)**	
				RR: 1.00 (0.76–1.31)	
Caan et al. (2006) [34]	3,057	Between 5 and 7 years	Recurrence	RR: 1.0 (0.7–1.3)	Stage, age, pre-diagnostic BMI, tamoxifen use, treatment, number of positive nodes, progesterone and oestrogen receptor status.
Soy food					
Boyapati et al. (2005) [41]	1,459	5.2 years	Breast cancer survival	HR: 0.99 (0.73–1.33)	Age at diagnosis, stage of disease, radiotherapy, ER/PR status and total energy intake.
Dietary fat					
Zhang et al. (1995) [47]	698	2.9 years	Breast cancer mortality	**RR: 2.5 (1.2–5.3)**	Age, cigarette smoking, education level, extent of disease, oestrogen receptor status and tumour size.
McEligot et al. (2006) [48]	516	6.67 years	All cause mortality	**HR: 3.12 (1.79–5.44)**	Stage of disease, age at diagnosis, BMI, parity, hormone replacement therapy use, alcohol use, multivitamin use, and energy intake.
Hebert et al. (1998) [49]	472	8–10 years	Breast cancer recurrence	**HR: 1.30 (1.03–1.64)** (consumption of butter, margarine, lard a day)	Stage, age, BMI, meat and beer consumption.
Saxe et al. (1999) [50]	149	> 5 years	Breast cancer recurrence	**HR: 1.46 (1.05–2.01)**	
			Breast cancer mortality	HR: 1.38 (0.99–1.91)	
Rohan et al. (1993) [51]	412	5.5 years	Breast cancer mortality	HR: 1.40 (0.66–2.96)	Energy, age at menarche, Quetelet index.
Chlebowski et al. (2006) [52]	2,437	5 years	Breast cancer recurrence	**HR: 0.71(0.53–0.94)**	Randomized group, ER status, tumour size, and surgery type.
Holmes et al. (1999) [53]	1,982	13.08 years	All cause mortality	RR: 1.21 (0.78–1.90)	Quantiles of nutrient or food intake prior to diagnosis, previous diet interval, age, diet interval, calendar year of diagnosis, body mass index, oral contraceptive use, menopausal status, postmenopausal hormone use, smoking, age at first birth and parity, number of metastatic lymph nodes, tumor size, and calories.
Kyogoku et al. (1992) [54]	212	Between 9 and 12 years	Breast cancer mortality	HR: 0.4 (0.1–1.3)	Clinical stage, body mass index, age at menarche, age at first birth, age at operation, radiation therapy, chemotherapy, endocrine therapy, operative procedure, total protein intake.
Other dietary micro- and macronutrients					

Table 2 continued

Author, year (reference)	No. of cases	Median length followed	Outcome	Relative risk/hazard ratio (95% CI) comparison of highest quartile/quintile vs lowest	Adjustment confounding variables
Kroenke et al. (2005) [57]	2,619	9 years	Breast cancer mortality	RR: 1.07 (0.66–1.63)	Age, time since diagnosis; body-mass index; energy intake, smoking, physical activity , diet missing in 1986, 1990, 1994, 1998, age at menarche, oral contraceptive use , birth index, menopausal status and use of postmenopausal hormone therapy , age at menopause , tamoxifen , chemotherapy; stage at diagnosis.
			Mortality from other causes	**RR: 0.54 (0.31–0.95)**	
Pierce et al. (2007) [58]	3,088	7.3 years	Breast cancer recurrence	HR: 0.96 (0.80–1.14)	Tumour stage, clinic site, age at randomization, anti-oestrogen use, and oophorectomy status.
			Breast cancer mortality	HR: 0.91 (0.72–1.15)	
Ingram (1994) [59]	103	6.75 years	Breast cancer mortality	Carotene: *P*-trend = 0.0012 Vitamin C: *P*-trend = 0.0286	
Fleischauer et al. (2003) [60]	220	Between 12 and 14 years	Breast cancer recurrence or mortality	HR: 0.54 (0.27–1.04)	Age at diagnosis, age at menopause, tumour stage, tamoxifen, radiation therapy use, hormone replacement therapy, smoking, exercise, and dietary intake of vitamin C or E.
Rock et al. (2005) [61]	1,551	7 years	Breast cancer recurrence	**HR: 0.57 (0.37–0.89)**	Age at diagnosis, clinical centre, plasma cholesterol, body mass index, tumour hormone receptors, and adjuvant chemotherapy.
Veronesi et al. (2006) [63]	1,739	14.6 years	Breast cancer recurrence	**HR: 0.62 (0.46–0.83)** (premenopausal) HR: 1.23 (0.63–2.40) (postmenopausal)	Menopausal status at randomization, type of surgery, pT and histology.
McDonald et al. (2002) [66]	125		Breast cancer mortality	**HR: 2.7 (1.3–5.58)**	Stage of disease at diagnosis, radiation therapy, and cigarette smoking.

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