



HAL
open science

Lifestyle changes and breast cancer prognosis: a review

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

► **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

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

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
© Springer Science+Business Media, LLC. 2008

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

E. Kellen (✉) · E. Van Limbergen
Universitaire Ziekenhuizen Leuven-LUCK,
Kapucijnenvoer 33, 3000 Leuven, Belgium
e-mail: eliane.kellen@uz.kuleuven.ac.be

G. Vansant
Department of Nutrition, Preventive Medicine,
Catholic University Leuven, Leuven, Belgium

G. Vansant
Department of Nutrition, Preventive Medicine,
University Hospital Gasthuisberg, Leuven, Belgium

M.-R. Christiaens · P. Neven · E. Van Limbergen
Multidisciplinary Breast Centre, University Hospitals Leuven,
Leuven, Belgium

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 phytoestrogens” “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 postmenopausal 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-positive receptors treated with the third generation aromatase 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 neuro-endocrine 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].

Phytoestrogens

Phytoestrogens 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 phytoestrogens may influence the effect of tamoxifen, a selective oestrogen receptor modulator, in breast cancer treatment either in an 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 bioavailable 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) of highest quartile/quintile vs lowest	comparison	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.
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.
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.
Obesity and weight gain after diagnosis						
Sagiv et al. (2007) [25]	1,273	5.8 years	Distant relapse-free survival	HR: 1.39 (0.72–2.68)		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.

Table 2 continued

Author, year (reference)	No. of cases	Median length followed	Outcome	Relative risk/hazard ratio (95% CI) of highest quartile/quintile vs lowest	comparison (95% CI)	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)		
Caan et al. (2006) [34]	3,057	Between 5 and 7 years	Recurrence	RR: 1.00 (0.76–1.31) 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) 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.
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.
Ingram (1994) [59]	103	6.75 years	Breast cancer mortality	HR: 0.91 (0.72–1.15)	
Fleischauer et al. (2003) [60]	220	Between 12 and 14 years	Breast cancer recurrence or mortality	Carotene: P -trend = 0.0012 Vitamin C: P -trend = 0.0286	
Rock et al. (2005) [61]	1,551	7 years	Breast cancer recurrence	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.
Veronesi et al. (2006) [63]	1,739	14.6 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.
McDonald et al. (2002) [66]	125		Breast cancer mortality	HR: 0.62 (0.46–0.83) (premenopausal) HR: 1.23 (0.63–2.40) (postmenopausal) HR: 2.7 (1.3–5.58)	Menopausal status at randomization, type of surgery, pT and histology. Stage of disease at diagnosis, radiation therapy, and cigarette smoking.

References

1. Parkin DM, Bray F, Ferlay J, Pisani P (2005) Global cancer statistics, 2002. *CA Cancer J Clin* 55:74–108
2. Key TJ, Verkasalo PK, Banks E (2001) Epidemiology of breast cancer. *Lancet Oncol* 2:133–140
3. World Cancer Research Fund/American Institute for Cancer Research (2007) Food, nutrition, physical activity, and the prevention of cancer: a global perspective. AICR, Washington
4. Duffy C, Perez K, Partridge A (2007) Implications of phytoestrogen intake for breast cancer. *CA Cancer J Clin* 57:260–277
5. Michels KB, Mohllajee AP, Roset-Bahmanyar E, Beehler GP, Moysich KB (2007) Diet and breast cancer: a review of the prospective observational studies. *Cancer* 109:2712–2749
6. Ha M, Mabuchi K, Sigurdson AJ et al (2007) Smoking cigarettes before first childbirth and risk of breast cancer. *Am J Epidemiol* 166:55–61
7. Caan B, Sternfeld B, Gunderson E, Coates A, Quesenberry C, Slattery ML (2005) Life After Cancer Epidemiology (LACE) Study: a cohort of early stage breast cancer survivors (United States). *Cancer Causes Control* 16:545–556
8. Irwin ML, Crumley D, McTiernan A et al (2003) Physical activity levels before and after a diagnosis of breast carcinoma: the Health, Eating, Activity, and Lifestyle (HEAL) study. *Cancer* 97:1746–1757
9. Lu W, Cui Y, Zheng Y et al (2007) Impact of newly diagnosed breast cancer on quality of life among Chinese women. *Breast Cancer Res Treat* 102:201–210
10. Pierce JP, Faerber S, Wright FA et al (2002) A randomized trial of the effect of a plant-based dietary pattern on additional breast cancer events and survival: the Women's Healthy Eating and Living (WHEL) Study. *Control Clin Trials* 23:728–756
11. Chlebowski RT, Blackburn GL, Buzzard IM et al (1993) Adherence to a dietary fat intake reduction program in postmenopausal women receiving therapy for early breast cancer. The Women's Intervention Nutrition Study. *J Clin Oncol* 11:2072–2080
12. Holmes MD, Chen WY, Feskanich D, Kroenke CH, Colditz GA (2005) Physical activity and survival after breast cancer diagnosis. *JAMA* 293:2479–2486
13. Holick CN, Newcomb PA, Trentham-Dietz A et al (2008) Physical activity and survival after diagnosis of invasive breast cancer. *Cancer Epidemiol Biomarkers Prev* 17:379–386
14. Abrahamson PE, Gammon MD, Lund MJ et al (2006) Recreational physical activity and survival among young women with breast cancer. *Cancer* 107:1777–1785
15. Enger SM, Bernstein L (2004) Exercise activity, body size and premenopausal breast cancer survival. *Br J Cancer* 90:2138–2141
16. Pierce JP, Stefanick ML, Flatt SW et al (2007) Greater survival after breast cancer in physically active women with high vegetable-fruit intake regardless of obesity. *J Clin Oncol* 25:2345–2351
17. Borugian MJ, Sheps SB, Kim-Sing C et al (2004) Insulin, macronutrient intake, and physical activity: are potential indicators of insulin resistance associated with mortality from breast cancer? *Cancer Epidemiol Biomarkers Prev* 13:1163–1172
18. Ligibel JA, Campbell N, Partridge A et al (2008) Impact of a mixed strength and endurance exercise intervention on insulin levels in breast cancer survivors. *J Clin Oncol* 26:907–912
19. Campbell KL, McTiernan A (2007) Exercise and biomarkers for cancer prevention studies. *J Nutr* 137:161S–169S
20. McTiernan A, Tworoger SS, Rajan KB et al (2004) Effect of exercise on serum androgens in postmenopausal women: a 12-month randomized clinical trial. *Cancer Epidemiol Biomarkers Prev* 13:1099–1105
21. Campbell KL, Westerlind KC, Harber VJ, Bell GJ, Mackey JR, Courneya KS (2007) Effects of aerobic exercise training on estrogen metabolism in premenopausal women: a randomized controlled trial. *Cancer Epidemiol Biomarkers Prev* 16:731–739
22. Adesanya OO, Zhou J, Samathanam C, Powell-Braxton L, Bondy CA (1999) Insulin-like growth factor 1 is required for G2 progression in the estradiol-induced mitotic cycle. *Proc Natl Acad Sci USA* 96:3287–3291
23. Holmes MD, Murin S, Chen WY, Kroenke CH, Spiegelman D, Colditz GA (2007) Smoking and survival after breast cancer diagnosis. *Int J Cancer* 120:2672–2677
24. Fentiman IS, Allen DS, Hamed H (2005) Smoking and prognosis in women with breast cancer. *Int J Clin Pract* 59:1051–1054
25. Sagiv SK, Gaudet MM, Eng SM et al (2007) Active and passive cigarette smoke and breast cancer survival. *Ann Epidemiol* 17:385–393
26. Manjer J, Andersson I, Berglund G et al (2000) Survival of women with breast cancer in relation to smoking. *Eur J Surg* 166:852–858
27. Sopori M (2002) Effects of cigarette smoke on the immune system. *Nat Rev Immunol* 2:372–377
28. Kendall A, Folkard EJ, Dowsett M (2007) Influences on circulating oestrogens in postmenopausal women: relationship with breast cancer. *J Steroid Biochem Mol Biol* 103:99–109
29. Terry PD, Rohan TE, Franceschi S, Weiderpass E (2002) Cigarette smoking and the risk of endometrial cancer. *Lancet Oncol* 3:470–480
30. Carmichael AR (2006) Obesity and prognosis of breast cancer. *Obes Rev* 7:333–340
31. Chlebowski RT (1994) Dietary fat intake reduction for patients with resected breast cancer. *Adv Exp Med Biol* 364:11–23
32. Chlebowski RT, Aiello E, McTiernan A (2002) Weight loss in breast cancer patient management. *J Clin Oncol* 20:1128–1143
33. Kroenke CH, Chen WY, Rosner B, Holmes MD (2005) Weight, weight gain, and survival after breast cancer diagnosis. *J Clin Oncol* 23:1370–1378
34. Caan BJ, Emond JA, Natarajan L et al (2006) Post-diagnosis weight gain and breast cancer recurrence in women with early stage breast cancer. *Breast Cancer Res Treat* 99:47–57
35. Byers T, Sedjo RL (2006) A weight loss trial for breast cancer recurrence: pre-menopausal, post-menopausal, both, or neither? *Cancer Causes Control* 17:1–3
36. McTiernan A, Rajan KB, Tworoger SS et al (2003) Adiposity and sex hormones in postmenopausal breast cancer survivors. *J Clin Oncol* 21:1961–1966
37. Griggs JJ, Sorbero ME, Lyman GH (2005) Undertreatment of obese women receiving breast cancer chemotherapy. *Arch Intern Med* 165:1267–1273
38. Carmichael AR, Bates T (2004) Obesity and breast cancer: a review of the literature. *Breast* 13:85–92
39. Dignam JJ, Wieand K, Johnson KA, Fisher B, Xu L, Mamounas EP (2003) Obesity, tamoxifen use, and outcomes in women with estrogen receptor-positive early-stage breast cancer. *J Natl Cancer Inst* 95:1467–1476
40. Messina M, Caskill-Stevens W, Lampe JW (2006) Addressing the soy and breast cancer relationship: review, commentary, and workshop proceedings. *J Natl Cancer Inst* 98:1275–1284
41. Boyapati SM, Shu XO, Ruan ZX et al (2005) Soyfood intake and breast cancer survival: a followup of the Shanghai Breast Cancer Study. *Breast Cancer Res Treat* 92:11–17
42. Limer JL, Speirs V (2004) Phyto-oestrogens and breast cancer chemoprevention. *Breast Cancer Res* 6:119–127
43. Wu AH, Pike MC, Williams LD et al (2007) Tamoxifen, soy, and lifestyle factors in Asian American women with breast cancer. *J Clin Oncol* 25:3024–3030

44. von SE, Rutqvist LE (2005) Menopausal hormone therapy after breast cancer: the Stockholm randomized trial. *J Natl Cancer Inst* 97:533–535
45. Holmberg L, Anderson H (2004) HABITS (hormonal replacement therapy after breast cancer—is it safe?), a randomised comparison: trial stopped. *Lancet* 363:453–455
46. Holm LE, Nordevang E, Hjalmar ML, Lidbrink E, Callmer E, Nilsson B (1993) Treatment failure and dietary habits in women with breast cancer. *J Natl Cancer Inst* 85:32–36
47. Zhang S, Folsom AR, Sellers TA, Kushi LH, Potter JD (1995) Better breast cancer survival for postmenopausal women who are less overweight and eat less fat. The Iowa Women's Health Study. *Cancer* 76:275–283
48. McEligot AJ, Largent J, Ziogas A, Peel D, Anton-Culver H (2006) Dietary fat, fiber, vegetable, and micronutrients are associated with overall survival in postmenopausal women diagnosed with breast cancer. *Nutr Cancer* 55:132–140
49. Hebert JR, Hurley TG, Ma Y (1998) The effect of dietary exposures on recurrence and mortality in early stage breast cancer. *Breast Cancer Res Treat* 51:17–28
50. Saxe GA, Rock CL, Wicha MS, Schottenfeld D (1999) Diet and risk for breast cancer recurrence and survival. *Breast Cancer Res Treat* 53:241–253
51. Rohan TE, Hiller JE, McMichael AJ (1993) Dietary factors and survival from breast cancer. *Nutr Cancer* 20:167–177
52. Chlebowski RT, Blackburn GL, Thomson CA et al (2006) Dietary fat reduction and breast cancer outcome: interim efficacy results from the Women's Intervention Nutrition Study. *J Natl Cancer Inst* 98:1767–1776
53. Holmes MD, Stampfer MJ, Colditz GA, Rosner B, Hunter DJ, Willett WC (1999) Dietary factors and the survival of women with breast carcinoma. *Cancer* 86:826–835
54. Kyogoku S, Hirohata T, Nomura Y, Shigematsu T, Takeshita S, Hirohata I (1992) Diet and prognosis of breast cancer. *Nutr Cancer* 17:271–277
55. Wynder EL, Taioli E, Rose DP (1992) Breast cancer—the optimal diet. *Adv Exp Med Biol* 322:143–153
56. Rock CL, Flatt SW, Thomson CA et al (2004) Effects of a high-fiber, low-fat diet intervention on serum concentrations of reproductive steroid hormones in women with a history of breast cancer. *J Clin Oncol* 22:2379–2387
57. Kroenke CH, Fung TT, Hu FB, Holmes MD (2005) Dietary patterns and survival after breast cancer diagnosis. *J Clin Oncol* 23:9295–9303
58. Pierce JP, Natarajan L, Caan BJ et al (2007) Influence of a diet very high in vegetables, fruit, and fiber and low in fat on prognosis following treatment for breast cancer: the Women's Healthy Eating and Living (WHEL) randomized trial. *JAMA* 298:289–298
59. Ingram D (1994) Diet and subsequent survival in women with breast cancer. *Br J Cancer* 69:592–595
60. Fleischauer AT, Simonsen N, Arab L (2003) Antioxidant supplements and risk of breast cancer recurrence and breast cancer-related mortality among postmenopausal women. *Nutr Cancer* 46:15–22
61. Rock CL, Flatt SW, Natarajan L et al (2005) Plasma carotenoids and recurrence-free survival in women with a history of breast cancer. *J Clin Oncol* 23:6631–6638
62. Goodwin PJ, Ennis M, Pritchard KI, Koo J, Trudeau ME, Hood N (2003) Diet and breast cancer: evidence that extremes in diet are associated with poor survival. *J Clin Oncol* 21:2500–2507
63. Veronesi U, Mariani L, Decensi A et al (2006) Fifteen-year results of a randomized phase III trial of fenretinide to prevent second breast cancer. *Ann Oncol* 17:1065–1071
64. Ladas EJ, Jacobson JS, Kennedy DD, Teel K, Fleischauer A, Kelly KM (2004) Antioxidants and cancer therapy: a systematic review. *J Clin Oncol* 22:517–528
65. D'Andrea GM (2005) Use of antioxidants during chemotherapy and radiotherapy should be avoided. *CA Cancer J Clin* 55:319–321
66. McDonald PA, Williams R, Dawkins F, Adams-Campbell LL (2002) Breast cancer survival in African American women: is alcohol consumption a prognostic indicator? *Cancer Causes Control* 13:543–549
67. Tapiero H, Townsend DM, Tew KD (2004) The role of carotenoids in the prevention of human pathologies. *Biomed Pharmacother* 58:100–110
68. Rock CL, Kusluski RA, Galvez MM, Ethier SP (1995) Carotenoids induce morphological changes in human mammary epithelial cell cultures. *Nutr Cancer* 23:319–333
69. Boffetta P, Hashibe M (2006) Alcohol and cancer. *Lancet Oncol* 7:149–156
70. Ballard-Barbash R, McTiernan A (2007) Is the whole larger than the sum of the parts? The promise of combining physical activity and diet to improve cancer outcomes. *J Clin Oncol* 25:2335–2337
71. Jones LW, Demark-Wahnefried W (2006) Diet, exercise, and complementary therapies after primary treatment for cancer. *Lancet Oncol* 7:1017–1026
72. Doyle C, Kushi LH, Byers T et al (2006) Nutrition and physical activity during and after cancer treatment: an American Cancer Society guide for informed choices. *CA Cancer J Clin* 56:323–353
73. Demark-Wahnefried W, Clipp EC, Lipkus IM et al (2007) Main outcomes of the FRESH START trial: a sequentially tailored, diet and exercise mailed print intervention among breast and prostate cancer survivors. *J Clin Oncol* 25:2709–2718
74. Sabatino SA, Coates RJ, Uhler RJ, Pollack LA, Alley LG, Zauderer LJ (2007) Provider counseling about health behaviors among cancer survivors in the United States. *J Clin Oncol* 25:2100–2106
75. Wold KS, Byers T, Crane LA, Ahnen D (2005) What do cancer survivors believe causes cancer? (United States). *Cancer Causes Control* 16:115–V23
76. Irwin ML (2006) Randomized controlled trials of physical activity and breast cancer prevention. *Exerc Sport Sci Rev* 34:182–193