Molecular Science

AIMS Molecular Science, 4(3): 252-270.
DOI: 10.3934/molsci.2017.3.252
Received 18 May 2017,
Accepted 12 July 2017,
Published 20 July 2017

http://www.aimspress.com/journal/Molecular

Review

Dietary influence on estrogens and cytokines in breast cancer

Xin Nian[1,3], Yasuhiro Nagai[1], Cameron Jeffers[1], Kara N. Maxwell[2], and Hongtao Zhang[1,*]

[1] Department of Pathology and Laboratory Medicine, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, Pennsylvania, 19104, USA
[2] Division of Hematology/Oncology, Department of Medicine, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, Pennsylvania, 19104, USA
[3] First Affiliated Hospital of Kunming Medical University, Kunming, Yunnan, 650032, China

* **Correspondence:** Email: zhanghon@mail.med.upenn.edu; Tel: (215) 573-9256; Fax: (215) 898-2401.

Abstract: Breast cancer affects one out of eight women in their lifetime. Many factors contribute to the development of breast cancer, such as hereditary mutations and lifetime exposure to environmental factors, including estrogen. In addition, overweight and obesity, especially with increased waist circumference, are known to be associated with breast cancer risk. This review will summarize our understanding of the effect of diet on breast cancer incidence and progression. Since some inflammatory cytokines that are changed by a high-fat diet are known to promote the growth of breast cancer cells, these cytokines may serve as biomarkers to monitor the dietary influence for women at high risk of breast cancer and as future therapeutic targets for breast cancer treatment.

Keywords: breast cancer; diets; estrogens; cytokines; fat; weight loss

Abbreviations: CI: confidence interval; COX: cyclooxygenase; ER: estrogen receptor; HER2: human epidermal growth factor 2 receptor; HGF: hepatocyte growth factor; HR = hazard ratio; NSAIDs: nonsteroidal anti-inflammatory drugs; PGE2: Prostaglandin E2; PR: progesterone receptor; PUFAs: Polyunsaturated fatty acids

1. Introduction

Breast cancer represents the most commonly diagnosed cancer in women. According to American Cancer Society (www.cancer.org), 252,710 new cases of invasive breast cancers are predicted to be

diagnosed in the USA in 2017, with an expected 40,610 deaths [1]. Familial diseases only account for 5–10% of breast cancer cases, while the majority of breast cancers are sporadic cancers that are induced by somatic mutations. A recent study estimated that in breast cancer the majority of somatic cancer-related mutations are due to random mistakes during normal DNA replication [2]. However, it is also clear the rate of random mutations is not entirely equivalent to the risk of cancers, since in most cases more than two mutations are needed to induce a cancer. A large percentage of breast cancer cancers are still preventable. Cancer research UK estimates that 27% of breast cancer cases could be prevented [3].

A number of lifestyle-related risk factors have been associated with breast cancer, including consumption of alcohol, being overweight or obese (particularly abundant abdominal adipose, measured as waist circumference), physical activity, post-menopausal exposure to hormone therapy, etc. Numerous studies have attempted to explain the association of diet with cytokines and breast cancer. We will first review the evidence and then discuss the influence of diets on cytokines that can contribute to the development of breast cancer.

2. Epidemiological studies on diets and breast cancer risk and progression

2.1. High-fat diets

The potential influence of a high-fat diet on the risk of development of breast cancer and subsequent progression has been evaluated in many studies. Two of the large prospective cohort studies are the Nurses' Health Study (NHS) and the Nurses' Health Study II (NHSII) [4]. The NHS was initiated in 1976 when 121,701 US female registered nurses ages 30–55 years completed an initial questionnaire. The NHSII was initiated in 1989 with 116,430 nurses ages 25–42 years. Diet was assessed every 4 years using a semi-quantitative food frequency questionnaire. One study compared the incidence of lethal cases, which were women with invasive breast cancer who died of breast cancer [5]. It was found that higher total fat intake was associated with a slightly lower breast cancer mortality risk (top vs. bottom quintile HR = 0.85; 95%CI 0.72–1.01; p trend = 0.05). However, among women diagnosed with breast cancer, pre-diagnosis fat intake had no effect on survival. Although the analysis failed to provide a solid support for a protective role for high fat intake, it strongly argued against a causal role for fat intake in increased mortality from breast cancer, as higher pre-diagnosis fat intake was not associated with increased risk of lethal breast cancer in these large prospective cohort studies [5].

It is possible that only certain components of a high-fat diet are associated with an increased risk of breast cancer. The NHSII study reported a positive association between animal fat intake and breast cancer risk among premenopausal women, but not among postmenopausal women [6]. Specifically, higher cholesterol intake and early adult intake of animal fat were associated with higher premenopausal breast cancer risk (highest vs. lowest quintile HR = 1.18; 95%CI 1.04–1.33, p trend = 0.01). In an ecologic study of 46 dietary surveys performed in 17 countries, intake of animal fat, but not fish fat, was associated with breast cancer mortality in women of 50 years and above. However, vegetable fat intake also correlated positively ($p < 0.01$) with breast cancer mortality [7].

If the high-fat diet represents a risk for breast cancer, low-fat diet might then bring benefit to the management of breast cancer. In the Women's Intervention Nutrition Study (WINS), a reduction in dietary fat intake to 22% of total energy intake led to a 24% reduction in the recurrence rate of breast cancer [8]. Patients in the reduced fat group maintained a reduced BMI with a 6-pound lower mean

body weight. A survival analysis was completed at the 108-month follow-up based on death registry information. Fewer deaths in the intervention group (HR 0.82, 95%CI 0.64–1.07) were noticed, although the difference was not statistically significant ($p = 0.146$) [9].

However, the Women's Healthy Eating and Living (WHEL) randomized trial reported no association of dietary fat reduction with recurrence or survival in women with early stage breast cancer [10]. In this study, women in the intervention group were encouraged to have more vegetable and fruit intake and reduce the energy intake from fat to 15–20% of total calories. Despite increased vegetable consumption was achieved in the intervention group, these subjects were only able to reduce fat intake to 21.2–22.7% of total energy during the first year, as compared to 28.5% at the baseline, but gradually gained back fat intake to 28.9% at 72 month.

One notable difference between the two contradictory studies was that weight loss was observed in the WINS study but not in WHEL. It is thus proposed that diet modifications (increasing fruit, vegetables, and fiber, while reducing fat intake) may significantly reduce breast cancer risk or increase relapse-free survival only if they are associated with weight loss.

As breast cancer is a disease of many causes and thus can be categorized into several subtypes, it is likely that fat intake in the diet is more associated with certain types of breast cancer. In a large ($n = 337,327$) heterogeneous cohort of women [11], 10,062 breast cancer cases were recorded during the 11.5-year follow-up. This study reported that high saturated fat were associated with greater risk of ER+PR+ (highest vs. lowest quintiles, HR = 1.28, 95%CI 1.09–1.52, p trend = 0.009) and HER2− disease (highest vs. lowest quintiles, HR = 1.29, 95%CI 1.01–1.64, p trend = 0.04). This result is consistent with the role of fat-induced estrogen activity in the development of ER+ breast cancer that we will discuss in later sections.

2.2. Dietary fatty acids

High-fat diets are complex and contain different types of fatty acids, and only some may be beneficial to reduce the risk to develop breast cancer. Without teasing out the different types of fatty acids, it could be difficult to come to a clear conclusion on the effect of total fatty acids on breast cancer. Not surprisingly, a meta-analysis of Embase and PubMed through September 2015, which identified twenty-four independent studies on dietary total fat and fatty acids intake and seven studies on serum fatty acids, failed to observe any association between dietary total fat/fatty acids intake and the risk of breast cancer [12].

A group of fatty acids called polyunsaturated fatty acids (PUFAs) contain more than one double bond in their backbone. For humans, essential fatty acids are either ω-3 or ω-6 PUFAs. Studies comparing the breast adipose tissue from breast cancer patients and controls demonstrated that age-adjusted ω-6 PUFA (linoleic acid and arachidonic acid) content was significantly higher in breast cancer patients (649 ± 36.00 vs. 527.6 ± 38.6, μmol/g, $p = 0.02$) [13]. In a prospective Shanghai Women's Health Study including 72,571 cancer-free participants at baseline, women with lowest intake of marine-derived ω-3 PUFA and highest intake of ω-6 PUFA had increased risk for breast cancer (HR = 2.06; 95%CI = 1.27–3.34), compared to women with highest intake of marine-derived ω-3 PUFAs and lowest intake of ω-6 PUFAs [14]. This is consistent with a similar observation on breast cancer risk previously reported in a prospective study of 35,298 Singapore Chinese women [15].

In other studies, ω-3 PUFAs were also reported to have benefits to reduce the mortality in breast

cancer patients. Khankari et al. examined a population-based follow-up study conducted on Long Island, New York, among 1463 women who were newly diagnosed with first primary breast cancer [16] that were followed for 14.7 years. These patients were interviewed approximately 3 months after diagnosis to assess risk and prognostic factors, including dietary intake. All-cause mortality was reduced among women who reported the highest intake of fish (other than tuna and shellfish) (HR = 0.71, 95%CI = 0.55–0.92, p = 0.03) and long-chain ω-3 PUFA DHA (HR = 0.71, 95%CI = 0.55–0.92, p = 0.04). Protective effect of long-chain ω-3 PUFA intake from fish and other dietary sources was also suggested by the Japan Collaborative Cohort (JACC) study [17]. In contrast, a later Japan Public Health Center-based prospective (JPHC) study indicated that ω-6 PUFA was associated with higher risk of tumors positive for the estrogen receptor (ER) and progesterone (PR) [18].

It is proposed that some of ω-6 PUFA, such as Arachidonic acid (AA), are pro -inflammatory and can produce prostaglandin E2 (PGE_2, see next section). In contrast, ω-3 Fatty acids, such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), bind to the same enzymes used in AA metabolism and therefore potentially lower the levels of inflammatory eicosanoids. In addition, the 3-series of PGs (PGE_3), which are synthesized after high ω-3 PUFA diets, are less efficient than PGE_2 to induce macrophages to produce the inflammatory cytokine IL-6 [19]. Furthermore, ω-3 PUFAs can also induce cytotoxic environment to increase apoptosis and reduce growth of transformed and malignant breast cancer cells [20].

2.3. Mediterranean diet

Since the overall cancer incidence in Mediterranean countries is lower than in other Western countries, such as UK and USA, the Mediterranean diet has been suspected to be beneficial to reducing cancer risk [21]. The Mediterranean diet is characterized with high consumption of vegetables, fruits, nuts, legumes, unprocessed cereals, and fish. The diet also contains a high ratio of monounsaturated fatty acids to saturated fatty acids, modest consumption of alcohol, and minimal consumption of meat and dairy products.

In a meta-analysis, women with high Mediterranean diet adherence slightly reduced risk of postmenopausal breast cancer as compared with women of low adherence [22] (HR = 0.94, 95%CI 0.88–1.01). Although the Mediterranean diet components of vegetables and fruits are both associated with reduced breast cancer risk in many studies, the consumption of alcohol is considered to be a risk factor [23] and could compromise the overall benefit. Not surprisingly, in a meta-analysis of published reports on Mediterranean diet and breast cancer risk, although a 10% reduced risk was observed for the diet in pooled case-control studies, no reduced risk was observed in prospective cohort studies [21]. An alternate Mediterranean Diet Score that excludes alcohol has been developed to evaluate the effect of Mediterranean diet [22].

Using the alternate Mediterranean Diet Score system, a recently published Netherlands Cohort Study, in which 62,573 women aged 55–69 years had been followed up for cancer incidence from 1986 to 2007, revealed that the risk of ER negative postmenopausal breast cancer was inversely associated with adherence to Mediterranean diet [22]. Compared with women who had low adherence to Mediterranean diet, high adherence women had 40% reduced risk of ER negative breast cancer (HR = 0.60, 95%CI 0.39–0.93, p for trend = 0.032). Very weak or no association with Mediterranean diet was found for ER positive as well as total breast cancer.

Mediterranean diet supplemented with extra-virgin olive oil appeared to show beneficial effect

in the prevention of breast cancer incidence in the PREDIMED study, which recruited 4282 women in Spain aged 60 to 80 years and at high cardiovascular disease risk [24]. The limitation for this secondary analysis is the low number of incident cases (only 35), and these women were all white, postmenopausal, and at high risk for cardiovascular disease. It is not clear if this observation can be extended to a broader population.

2.4. Other diets

The Mediterranean diet includes fruits and vegetables as two beneficial components for health. Both fruits and vegetables have been examined in many studies to evaluate their benefit. In the Nurses' Health Study II (NHSII) study, high fruit consumption (2.9 vs. 0.5 servings per day) during adolescence was associated with 25% lower risk of breast cancer diagnosed in middle age. Higher early adulthood intake of fruits and vegetables rich in alpha carotene was also associated with 18% lower risk of premenopausal breast cancer [25].

Liu et al. also studied the relationship between adolescent diet and subsequent risk of breast cancer. Dietary fiber, vegetable protein, vegetable fat, and nuts consumed during adolescence were associated with 20–34% reduced breast cancer risk [26].

Despite the potential benefit of fruit intake in adolescence, its effect on breast cancer is very limited, especially when attempted to use as a therapeutic approach. In the WHEL randomized trial with women previously treated for early stage breast cancer [10], the adoption of a diet that was very high in vegetables, fruit, and fiber and low in fat failed to reduce subsequent breast cancer events or mortality during a 7.3-year follow-up period.

2.5. Factors that complicate the dietary effect

Understanding the effect of diets from epidemiological studies is very challenging. One major issue is the reliability of food diary, if the study is based on questionnaires tracking down what volunteers have consumed, and especially if the food diary is based on the recollection. It is known that study participants have variability in the accuracy of reporting what they eat in prospective trials. In addition, it is practically difficult to have a "control" group for the diet. Some food or food supplements that might also be functional are difficult to be controlled and thus can mask the effect of the studied diet.

2.5.1. Alcohol

Alcohol is a known risk factor for breast cancer. The unequivocal finding is that the breast cancer risk is increased by alcohol, with a 13% increase for each additional daily drink [27]. A study of the UK Dietary Cohort Consortium reported that a 'high-alcohol' pattern was associated with a higher risk of breast cancer (HR = 1.27, 95%CI 1.00–1.62, p trend = 0.04), especially in post-menopausal women (HR = 1.46, 95%CI 1.08–1.98, p trend = 0.01) [23]. However, modest alcohol is considered a beneficial factor in the Mediterranean diet. In the Netherlands Cohort Study, when the breast cancer incidence was evaluated using an alcohol-excluding Mediterranean diet score, women who had 4–5 points had reduced age-adjusted risk of breast cancer incidence, as compared with those with 0–3 points (HR = 0.85, 95%CI 0.74–0.98). In contrast, when having modest alcohol

scored one point, the benefit of Mediterranean diet to the reduction of breast cancer incidence was no longer significant (HR = 0.92, 95%CI 0.79–1.06) [22].

2.5.2. Glycemic index (GI)

Dong et al. conducted a meta-analysis of prospective cohort studies to evaluate the associations between dietary glycemic index (GI)/glycemic load (GL) and risk of breast cancer [28]. The meta-analysis suggested that high dietary GI is associated with a significantly increased risk of breast cancer. Dietary GL was not associated with breast cancer risk.

2.5.3. Red meat and processed meat.

Processed meat is classified by the International Agency for Research on Cancer (IARC) of World Health Organization (WHO) as carcinogenic, and red meat is also considered as probably carcinogenic by the same agency. A recent study [29] showed that high consumption of red meat and processed meat may increase risk of postmenopausal breast cancer.

3. Mechanism by which dietary factors influence breast cancer risk

There are a number of possible ways in which dietary factors may modulate breast cancer risk, such as through modulation of cholesterol levels, body weight, and inflammatory cytokines. Furthermore, it is likely these factors interact to contribute to breast cancer risk. Obesity is associated with chronic inflammation that also contributes to the proliferation of cancer cells or the escape of cancer cells from immune surveillance, diets can influence the development of cancers by modulating the activity of inflammatory cytokines. For breast cancer, some cytokines can further regulate the production of estrogens in the microenvironment.

3.1. Epidemiological relationship between cholesterol levels and breast cancer risk

Since high-fat diets can increase circulating cholesterol levels, many epidemiological studies have been performed to evaluate the association between blood cholesterol level and breast cancer risk. These studies, however, have failed to produce consistent conclusions. There are many possible explanations, including confounding effects of statin use, study heterogeneity regarding breast cancer subtypes, and the potential differential effects of HDL cholesterol (HDL-C), LDL-cholesterol (LDL-C), and triglycerides (TG). In addition, it is suggested that some of these studies were compromised by potential preclinical bias, which in the case of breast cancer refers to the influence of cancer cells on blood cholesterol levels [30]. Malignant cells are known to have increased LDL receptor activity and consume the metabolites of cholesterol as the fuel for growth. This may drive down the serum level of cholesterol. Therefore, a well - designed epidemiological study should take this into consideration and ideally exclude the cancer cases diagnosed during the first years of follow-up.

In general, cholesterol levels appear to be negatively associated with breast cancer risk. In a study of a cohort of 46,570 Swedish women less than 75 years of age, serum cholesterol levels were not found to have any correlation with breast cancer risks [31]. However, in women younger than 50 years old, there was a significantly decreased risk with increasing serum cholesterol levels. Since the first

statin drug was approved in 1987, cholesterol levels in the Tornberg study should not be affected by concomitant statin use in the study participants. Total serum cholesterol was also observed to be inversely associated with breast cancer risk in a Norwegian study [32]. In this study, 24,329 Norwegian women were followed for 11–14 years and 242 cancer cases were recorded. Women in the highest quartile of serum cholesterol (> 7.51 mM) had a 47% reduced risk of breast cancer than those in the lowest quartile (< 5.85 mM), and strong association became obvious after 2 years. There was an overall weak negative association for serum triglycerides with breast cancer risk [32].

It appears that serum HDL-C is the more relevant form of cholesterol in terms of influence on breast cancer risk. In a meta-analysis of reported studies up to 2014, a reversed association of total cholesterol with breast cancer risk was observed in studies that excluded preclinical bias [30]. In this study, LDL-C was not associated with breast cancer risk, and HDL-C was the specific type of cholesterol that is negatively associated with the risk.

The modest "protective" role of HDL-C in breast cancer was unexpected, but it can be explained by the changed estrogen and cytokine profiles in people with high HDL-C. In overweight and obese women, higher serum HDL-C was associated with reduced salivary estradiol concentration. In contrast, women who had high serum LDL-C/HDL-C ratio (≥ 2.08; 75 percentile) usually had substantially higher levels of salivary estradiol by cycle days. In addition, serum HDL-C was also inversely related to serum leptin and insulin [33], two cytokines that have influence on breast cancers (see later sections).

While the above studies suggest a protective role for total cholesterol, specifically due to HDL-C, two Korean studies have demonstrated a positive association between total cholesterol and breast cancer risk [34,35].

Despite the beneficial effect of serum cholesterol to breast cancer, dietary cholesterol intake has been associated with breast cancer risk. In a meta-analysis study, people with the highest dietary cholesterol intake had 29% higher risk than the lowest group to have breast cancer. The association between dietary cholesterol and breast cancer became statistically significant when the cholesterol intake was greater than 370 mg/day [36].

3.2. Possible mechanism of cholesterol on breast cancer risk

Cholesterol is the precursor for a large number of metabolites with important biological functions that may influence breast cancer risk and progression. It is reported that a metabolite of cholesterol, oxysterol 27-hydroxycholesterol (27HC), has estrogen receptor agonistic activity [37]. 27HC was also demonstrated to stimulate the growth and metastasis of tumors in several models of breast cancer. The enzyme responsible for the production of 27HC from cholesterol, CYP27A1, is observed to have elevated expression in breast tumors [37]. Thus, breast cancer cells have the potential to convert cholesterol into ER agonist to promote the proliferation of cancer cells.

3.3. Epidemiological relationship between obesity and breast cancer risk

In epidemiological studies, overweight/obese postmenopausal women have an increased risk of breast cancer incidence by as much as 40% [38,39]. In premenopausal women, studies suggested a decreased risk of breast cancer in overweight/obese women as defined by BMI [40]. However, the BMI might not be an ideal measurement for overweight/obese. When waist circumference was used

to measure abdominal adiposity, analysis of the data collected from the NHSII study indicated that waist circumference was significantly associated with greater incidence of breast cancer [41].

In breast cancer patients, studies have demonstrated that obesity is associated with a 35–40% increased risk of breast cancer recurrence and death, specifically in estrogen receptor-positive breast cancer [42,43]. As revealed by the analysis data collected from 80,000 women in 70 clinical trials (the Early Breast Cancer Trialists' Collaborative Group), obesity in premenopausal and perimenopausal women with estrogen receptor-positive breast cancer is associated with higher mortality rate [44]. In premenopausal women with ER-positive breast cancer, the cancer mortality rate was 21.5% after 10 years in obese women, but only 16.6% in normal-weight women with the disease.

3.4. Possible mechanisms of obesity on breast cancer risk

Overweight and obese individuals have a unique cytokine pattern that reflects typical products produced by adipocytes. These cytokines, termed adipocytokines, include inflammatory cytokines IL-6 and IL-8, the angiogenic cytokine VEGF, and the metabolic regulators insulin, insulin-like growth factors (IGF-1), adiponectin, leptin, resistin and visfatin [45] (Figure 1).

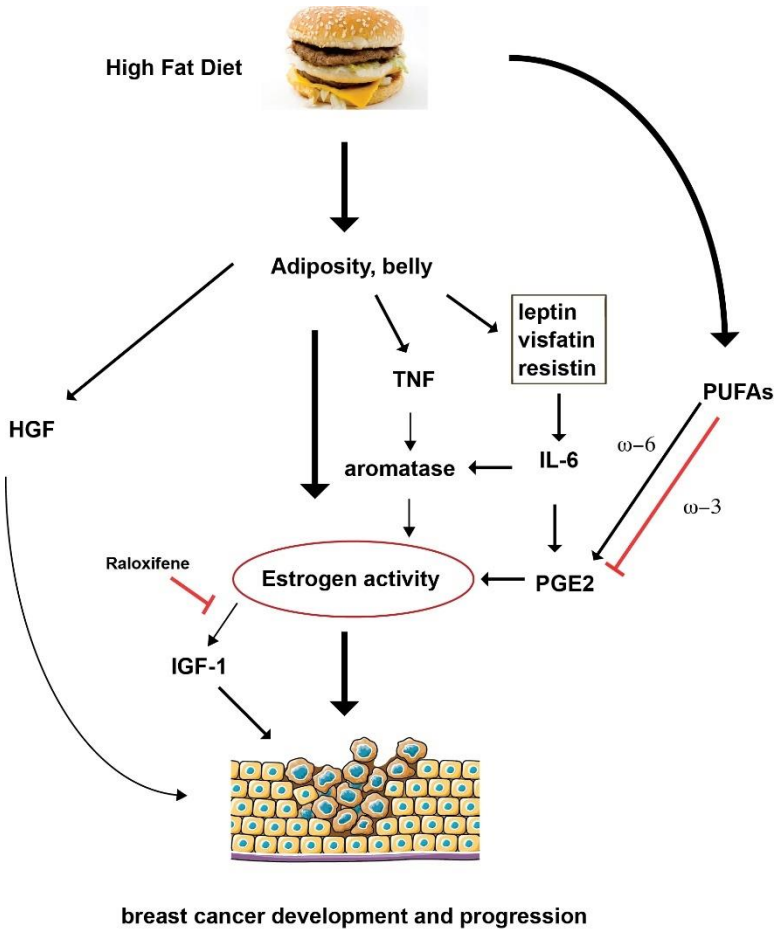

Figure 1. Fat diets, cytokine and breast cancer. High fat diets can affect adipocytokine production in the host. Some of these adipocytokines, as well as the fatty acids from the diets, have been shown to influence the development and progression of breast cancer.

Overweight and obesity may also influence the development of the breast cancer through the elevated levels of estrogen activity and increased levels of adipocyte-secreted endocrine factors [45]. For ER+ breast cancer, abundant estrogen activity has been shown to promote the growth of tumor cells.

In fat tissue, the estrogen is produced by the enzyme aromatase. One possible mechanism for inflammatory cytokines is to increase the aromatase function. Some cytokines, such as TNFα, IL-6, IL-11, leukemia inhibitory factor (LIF) and oncostatin M, are able to induce the expression of aromatase [46], thus eventually leading to increased estrogen activity.

3.4.1. Insulin-like growth factors (IGF)

Creighton and colleagues examined the effects of obesity on the gene expression of primary breast tumors [47]. An IGF signaling pattern was detected in obese breast cancer patients. It has also demonstrated that estrogens can induce an obesity-associated transcriptional program *in vitro*. This study highlighted the IGF activity as the consequence of obesity-related metabolism changes and the association between obesity and overproduction of estrogen.

IGF-1 is expected to promote cell proliferation and survival via the activation of phosphatidylinositol 3-kinase (PI3K)/Akt and mitogen-activated protein kinase (MAPK)/p38 signaling pathways. IGFs can also render resistance against therapeutic treatments [48].

Initial studies revealed that breast cancer patients had elevated circulating levels for IGF-I and for the major IGF-binding protein IGFBP3 [49]. Levels of both IGF-I and IGFBP3 are associated with tumor size. Patients with lower plasma IGF-I levels (< 120 ng/mL) had better overall survival. However, further studies, including prospective studies and meta-analysis, have indicated that there is a lack of strong evidence for IGF-1 and IGFB3 as a biomarker for breast cancer risk [50-55]. While IGF-1 may be associated with a subcategory of breast cancer, inconsistence in the detection methods of IGF-1 and IGFBP3 may have compromised previous studies to draw conclusions on serum/plasma IGF-1 and IGFBP3 [56]. In addition, insulin resistance might be more relevant to the development of hyperplasia and breast cancer in postmenopausal women [57].

Interestingly, administration of the anti-estrogen agent Raloxifene in postmenopausal high-risk women was shown to reduce serum IGF-1 in a dose-dependent manner [58]. This study also confirms that IGF-1 is down-stream of estrogens.

3.4.2. Insulin

In postmenopausal women, elevated baseline insulin levels were associated with higher risk to develop breast cancer, while glucose levels have no association with risk [59]. In early breast cancer patients, baseline insulin levels at diagnosis correlates with distant recurrence and death during the first 5 years, while obesity-related variables (BMI, weight, leptin) predict adverse outcome throughout the median 12.1 years of follow-up [60].

Studies suggest that insulin resistance is more directly linked to higher risk to develop breast cancer [61]. The homeostasis model assessment of insulin resistance (HOMA-IR) is a conventional method to assess insulin resistance. As shown in a cross-sectional study, the prevalence of breast cancer is higher in insulin-resistant patients than in insulin sensitive patients [61]. Individuals with insulin resistance (HOMA-IR ≥ 2.50) had higher risk of both premenopausal and postmenopausal

breast cancer (premenopausal: HR 1.98, 95%CI 1.19–3.32; postmenopausal: HR 1.29, 95%CI 1.01–1.63).

3.4.3. Resistin

Resistin is an adipocytokine of the cysteine-rich family of proteins mainly produced by macrophages. *In vitro* studies have shown that resistin stimulates invasion and migration of breast cancer cells through the phosphorylation of c-Src, protein phosphatase 2A (PP2A), and PKCα[62].

In a hospital-based case-control study, plasma resistin levels were associated with breast cancer risk in women, showing about two-fold higher risk for women in the highest quartiles of resistin [63]. Further analysis indicated that mean serum resistin was significantly higher in post-menopause breast cancer patients than controls and patients with benign breast lesion ($p < 0.001$) [64]. However, in premenopausal women, resistin may have a protective role in breast cancer [65].

3.4.4. Visfatin

Visfatin, also known as pre-B cell colony-enhancing factor (PBEF), is an inflammatory cytokine that is produced by fat cells. As shown in a rat model of high-fat diet induced non-alcoholic fatty liver disease (NAFLD), expression of visfatin in liver was also elevated [64]. In postmenopausal women, a positive relationship was found between serum visfatin level and dietary SFA, PUFA and cholesterol intake [66].

In a case-control study, significantly elevated serum level was found in postmenopausal breast cancer (PBC) cases than in control participants ($p < 0.001$) [67]. Women in the highest quartile of visfatin concentration had significantly higher risk for PBC (HR = 7.93; 95%CI 2.52–24.9). In breast cancer, high visfatin expression in tissue was associated with malignancy and poor patient survival [68].

An *in vitro* study indicated that curcumin, a known dietary NF-κB inhibitor, could reduce visfatin expression [69]. This can be explained by the existence of NF-κB binding sites in the promoter region of the visfatin gene [69]. In the animal model of NAFLD, high fat diet induced liver expression of visfatin was reduced by the treatment of curcumin [70]. In high-fat-induced obesity rats, both metformin and swimming exercise down-regulated visfatin levels in subcutaneous adipose tissue and peri-renal adipose tissue [71].

3.4.5. Leptin

Leptin is the protein product of the obese gene. In both rodents and man, plasma leptin levels correlate with BMI, and its level in obese people could be reduced after weight loss due to food restriction [72]. Both low-fat and low-carbohydrate diets for weight loss purpose have the same leptin-reducing effect in overweight-to-obese post-menopausal breast cancer survivors [73]. In ER negative breast cancer cells, leptin induced IL-6 production and the activation of Signal Transducer and Activator of Transcription 3 (STAT3) [74].

3.4.6. IL-6

In a cross-sectional study of 100 Korean adults free from pre-existing inflammatory disease or

cancer, serum CRP, TNF-α and IL-6 concentrations were found to be higher in obese than in non-obese individuals. Specially, obesity measured by visceral adiposity was significantly correlated with IL-6 concentration [75]. IL-6 from obese serum was shown to induce PGE production in cancer cells and subsequently aromatase expression in adipocytes to produce more estrogens [76].

In a randomized controlled trial, a caloric-restriction diet led to an average of 8.5% weight loss and a reduction in serum IL-6 levels [77].

3.4.7. CCL5

Chemokine (C-C motif) ligand 5 (CCL5), also known as RANTES, is a member of the CC chemokine family. CCL5 is a strong chemo-attractant for monocytes and T-cells to infiltrate to tumor, but it can also act directly on cancer cells. By binding to the CCR5 receptor, CCL5 was shown to increase glucose uptake by up-regulating cell surface expression of the glucose transporter GLUT1, and therefore increase ATP production in breast cancer cells [78]. Thus, the CCL5–CCR5 interaction in the tumor microenvironment was considered to regulate glycolysis to promote tumor proliferation and invasion.

The extracellular *in vivo* levels of CCL5, as determined by micro-dialysis, were three times higher within the breast cancer than in adjacent normal breast tissue [79]. In stage II breast cancer patients, CCL5 is a predictor of disease progression, as CCL5 levels are elevated in patients with high-grade tumors [80]. Expression of CCL5 in peritumoral adipose tissue of women with TNBC was shown to be associated with lymph node and distant metastases. There was also a negative correlation between CCL5 staining in the peritumoral adipose tissue and overall survival of patients [81].

Production of CCL5 is also linked to adiposity and estrogen activity. Serum levels of CCL5 in nonalcoholic fatty liver disease (NAFLD) are elevated as compared with normal healthy people [82]. In a rat model, it was observed that hepatic CCL5 was upregulated after only 4 weeks of high-fat-diet (HFD) [82]. CCL5 levels also correlated significantly with plasma estradiol concentrations, and the increased release of CCL5 by estradiol was confirmed by experimental mouse model of breast cancer [79]. CCL5 represents a potential target for breast cancer therapy.

3.4.8. Hepatocyte growth factor (HGF)

Adipocytes from obese subjects secret more HGF than those from lean subjects. At 6 months after bariatric surgery, serum HGF levels in obese subjects could reduce from an average of 1164 to 529 pg/mL [83].

Basal-like breast cancer (BBC) cells express the HGF receptor, c-Met. Sundaram et al. studied C3(1)-TAg mice, a murine model of BBC [84]. In this model, obesity-induced stable HGF expression and the phenotype were both maintained after several passages in the absence of dietary stimulation. Conditioned media from primary tumor fibroblasts of obese mice contained HGF and were able to stimulate tumor cell proliferation, while neutralization with anti-HGF antibody could prevent tumor cell migration.

3.4.9. Pro-inflammation prostaglandin PGE2

Prostaglandin E_2 (PGE_2) is a naturally occurring prostaglandin that has a role in increasing

vascular permeability, fever generation, and hyperalgesia. PGE2 is the metabolite of arachidonic acid, generated by an enzymatic cascade controlled by cyclooxygenase (COX) enzymes (e.g. COX2).

Upregulation of COX2 and, consequently, elevated PGE_2 synthesis are associated with the progression of many cancers, including breast cancer [85]. In breast carcinomas, COX2 expression also correlates with tumor size, high-grade HER2 positivity, and a worse disease-free interval. PGE_2 has also been associated with increased breast cancer risk, and several studies have indicated that the use of nonsteroidal anti-inflammatory drugs (NSAIDs), inhibitors of COX2, can reduce the risk of breast cancer in preclinical studies [86].

Both the adipose tissue and breast tumors can produce PGE2 to drive aromatase expression and accumulate estrogen locally in the breast [87]. Serum from obese postmenopausal women was shown to induce COX-2 expression and PGE2 production in breast cancer cells in an IL6-dependent manner [76].

4. The future for diets and dietary elements for breast cancer prevention and management

Evidence suggests that diets leading to weight loss may significantly reduce breast cancer recurrence risk and increase relapse-free survival [8]. These dietary modifications include increasing fruit, vegetables, and fiber, and reducing fat and alcohol intake.

A few dietary elements are positioned to supplement the standard of care for breast cancer patients. Although some of them have been tested in clinical trials [88], there are still insufficient evidences from interventional randomized control trials. Although the survival benefit remains to be the gold standard to evaluate the effect of therapies or dietary interventions, it is hoped that in the future biomarkers can be used as surrogate endpoints to facilitate clinical trials.

For the prevention of breast cancer, a short-term trial (1–2 years) sometimes is performed to predict the long-term effect of diets by monitoring the change of breast cancer risk factors, such as mammographic density [89].

In a 5-month intervention trial, Kaaks et al. studied the effects of dietary intervention in postmenopausal women with elevated baseline plasma testosterone levels. The diet included reductions in the intake of total fat and refined carbohydrates, an increase in the ratio of ω-3 over ω-6 and saturated fatty acids, and increased intake of foods rich in dietary fiber and phytoestrogens [90]. These dietary alterations led to a significant reduction of body weight, waist circumference, fasting serum levels of testosterone, C peptide, glucose, and insulin area (after glucose tolerance test). They also led to a significant increase of serum levels of sex hormone-binding globulin, IGFBP-1, IGFBP-2, and growth hormone-binding protein, although the serum levels of IGF-I were not changed [90].

A recent study indicates that a fasting-mimicking diet could reduce serum IGF-1 [91]. This study was performed in 100 generally healthy participants for the effects of a diet low in calories, sugars, and protein but high in unsaturated fats. The subjects were only on the fasting-mimicking diet for 5 consecutive days per month. After three months, in addition to the reduced serum IGF-1, body mass index, blood pressure, fasting glucose, triglycerides, total and low-density lipoprotein cholesterol, and C-reactive protein were more beneficially affected in participants at risk for diseases.

It is expected that dietary modification might be more beneficial to a subgroup of women. For example, in a clinical trial involving postmenopausal women with high breast density and increased risk for breast cancer, administration of ω-3 fatty acids increased serum DHA levels, but corresponding breast density changes only happened in women with BMI > 29 [92].

In addition to diets, exercise may lead to beneficial effects on serum inflammatory cytokines. In one study, women with diabetes who performed exercise regularly had a 59% reduced breast cancer risk [93]. In another study, the exercise group of postmenopausal breast cancer survivors was encouraged to achieve an average of 120 min/week of moderate to vigorous-intensity recreational activity over 6 months. Both insulin and IGF-1 levels were reduced in the exercise group (7.1 and 3.4%, respectively), while both of these two cytokines increased in the control group at the 6-month follow-up [94].

5. Conclusion

Over the past 20 years, US has seen a rising breast cancer incidence rate but lowering mortality rate. Both the early detection of breast cancer and the development of more advanced therapies account for these trends. As a result, more women now are living with breast cancer. It is clear that current accumulated knowledge of the effect of diets and other life styles such as exercise on breast cancer will be translated into practice. Diets may influence the risk of breast cancer recurrence or progression. In addition, some diets may also help decrease risk of development of breast cancer in the currently healthy population. An important public health implication is that the control of body fat, through proper dietary management and sufficient exercise, is beneficial to the reduction of the breast cancer risk, including the risk for disease recurrence and progression.

Acknowledgements

This work was supported by grants from the Breast Cancer Research Foundation and the National Institutes of Health to M.I.G. (R01CA089481, R01CA149425), the DOD IDEA grant to S.S. (W81XWH-15-1-0362), and the Paul Calabresi Career Development Award for Clinical Oncology (K12) to K.N.M.

Conflict of interest

The authors declare no conflict of interest.

References

1. Howlader N, Noone A, Krapcho M, et al. (2015) SEER Cancer Statistics Review, 1975–2012, National Cancer Institute. Bethesda, MD. 2015.
2. Tomasetti C, Li L, Vogelstein B (2017) Stem cell divisions, somatic mutations, cancer etiology, and cancer prevention. *Science* 355: 1330-1334.
3. Cancer Research UK, Statistics on preventable cancers. 2017. Available from: http://www.cancerresearchuk.org/health-professional/cancer-statistics/risk/preventable-cancers#heading-One
4. Colditz GA, Hankinson SE (2005) The Nurses' Health Study: lifestyle and health among women. *Nat Rev Cancer* 5: 388-396.
5. Boeke CE, Eliassen AH, Chen WY, et al. (2014) Dietary fat intake in relation to lethal breast cancer in two large prospective cohort studies. *Breast Cancer Res Treat* 146: 383-392.

6. Farvid MS, Cho E, Chen WY, et al. (2014) Premenopausal dietary fat in relation to pre- and post-menopausal breast cancer. *Breast Cancer Res Treat* 145: 255-265.
7. Sasaki S, Horacsek M, Kesteloot H (1993) An ecological study of the relationship between dietary fat intake and breast cancer mortality. *Prev Med* 22: 187-202.
8. 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.
9. Chlebowski RT (2013) Nutrition and physical activity influence on breast cancer incidence and outcome. *Breast* 22 Suppl 2: S30-37.
10. 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.
11. Sieri S, Chiodini P, Agnoli C, et al. (2014) Dietary fat intake and development of specific breast cancer subtypes. *J Natl Cancer Inst* 106.
12. Cao Y, Hou L, Wang W (2016) Dietary total fat and fatty acids intake, serum fatty acids and risk of breast cancer: A meta-analysis of prospective cohort studies. *Int J Cancer* 138: 1894-1904.
13. Bagga D, Anders KH, Wang HJ, et al. (2002) Long-chain n-3-to-n-6 polyunsaturated fatty acid ratios in breast adipose tissue from women with and without breast cancer. *Nutr Cancer* 42: 180-185.
14. Murff HJ, Shu XO, Li H, et al. (2011) Dietary polyunsaturated fatty acids and breast cancer risk in Chinese women: a prospective cohort study. *Int J Cancer* 128: 1434-1441.
15. Gago-Dominguez M, Yuan JM, Sun CL, et al. (2003) Opposing effects of dietary n-3 and n-6 fatty acids on mammary carcinogenesis: The Singapore Chinese Health Study. *Br J Cancer* 89: 1686-1692.
16. Khankari NK, Bradshaw PT, Steck SE, et al. (2015) Dietary intake of fish, polyunsaturated fatty acids, and survival after breast cancer: A population-based follow-up study on Long Island, New York. *Cancer* 121: 2244-2252.
17. Wakai K, Tamakoshi K, Date C, et al. (2005) Dietary intakes of fat and fatty acids and risk of breast cancer: a prospective study in Japan. *Cancer Sci* 96: 590-599.
18. Kiyabu GY, Inoue M, Saito E, et al. (2015) Fish, n - 3 polyunsaturated fatty acids and n - 6 polyunsaturated fatty acids intake and breast cancer risk: The Japan Public Health Center-based prospective study. *Int J Cancer* 137: 2915-2926.
19. Bagga D, Wang L, Farias-Eisner R, et al. (2003) Differential effects of prostaglandin derived from omega-6 and omega-3 polyunsaturated fatty acids on COX-2 expression and IL-6 secretion. *Proc Natl Acad Sci U S A* 100: 1751-1756.
20. Chenais B, Blanckaert V (2012) The janus face of lipids in human breast cancer: how polyunsaturated Fatty acids affect tumor cell hallmarks. *Int J Breast Cancer* 2012: 712536.
21. Schwingshackl L, Hoffmann G (2016) Does a Mediterranean-Type Diet Reduce Cancer Risk? *Curr Nutr Rep* 5: 9-17.
22. van den Brandt PA, Schulpen M (2017) Mediterranean diet adherence and risk of postmenopausal breast cancer: results of a cohort study and meta-analysis. *Int J Cancer* 140: 2220-2231.
23. Pot GK, Stephen AM, Dahm CC, et al. (2014) Dietary patterns derived with multiple methods from food diaries and breast cancer risk in the UK Dietary Cohort Consortium. *Eur J Clin Nutr* 68: 1353-1358.

24. Toledo E, Salas-Salvado J, Donat-Vargas C, et al. (2015) Mediterranean Diet and Invasive Breast Cancer Risk Among Women at High Cardiovascular Risk in the PREDIMED Trial: A Randomized Clinical Trial. *JAMA Intern Med* 175: 1752-1760.
25. Farvid MS, Chen WY, Michels KB, et al. (2016) Fruit and vegetable consumption in adolescence and early adulthood and risk of breast cancer: population based cohort study. *BMJ* 353: i2343.
26. Liu Y, Colditz GA, Cotterchio M, et al. (2014) Adolescent dietary fiber, vegetable fat, vegetable protein, and nut intakes and breast cancer risk. *Breast Cancer Res Treat* 145: 461-470.
27. Dam MK, Hvidtfeldt UA, Tjonneland A, et al. (2016) Five year change in alcohol intake and risk of breast cancer and coronary heart disease among postmenopausal women: prospective cohort study. *BMJ* 353: i2314.
28. Dong JY, Qin LQ (2011) Dietary glycemic index, glycemic load, and risk of breast cancer: meta-analysis of prospective cohort studies. *Breast Cancer Res Treat* 126: 287-294.
29. Inoue-Choi M, Sinha R, Gierach GL, et al. (2016) Red and processed meat, nitrite, and heme iron intakes and postmenopausal breast cancer risk in the NIH-AARP Diet and Health Study. *Int J Cancer* 138: 1609-1618.
30. Touvier M, Fassier P, His M, et al. (2015) Cholesterol and breast cancer risk: a systematic review and meta-analysis of prospective studies. *Br J Nutr* 114: 347-357.
31. Tornberg SA, Holm LE, Carstensen JM (1988) Breast cancer risk in relation to serum cholesterol, serum beta-lipoprotein, height, weight, and blood pressure. *Acta Oncol* 27: 31-37.
32. Vatten LJ, Foss OP (1990) Total serum cholesterol and triglycerides and risk of breast cancer: a prospective study of 24,329 Norwegian women. *Cancer Res* 50: 2341-2346.
33. Furberg AS, Jasienska G, Bjurstam N, et al. (2005) Metabolic and hormonal profiles: HDL cholesterol as a plausible biomarker of breast cancer risk. The Norwegian EBBA Study. *Cancer Epidemiol Biomarkers Prev* 14: 33-40.
34. Ha M, Sung J, Song YM (2009) Serum total cholesterol and the risk of breast cancer in postmenopausal Korean women. *Cancer Causes Control* 20: 1055-1060.
35. Kitahara CM, Berrington de Gonzalez A, Freedman ND, et al. (2011) Total cholesterol and cancer risk in a large prospective study in Korea. *J Clin Oncol* 29: 1592-1598.
36. Li C, Yang L, Zhang D, et al. (2016) Systematic review and meta-analysis suggest that dietary cholesterol intake increases risk of breast cancer. *Nutr Res* 36: 627-635.
37. McDonnell DP, Park S, Goulet MT, et al. (2014) Obesity, cholesterol metabolism, and breast cancer pathogenesis. *Cancer Res* 74: 4976-4982.
38. Reeves GK, Pirie K, Beral V, et al. (2007) Cancer incidence and mortality in relation to body mass index in the Million Women Study: cohort study. *BMJ* 335: 1134.
39. Renehan AG, Zwahlen M, Egger M (2015) Adiposity and cancer risk: new mechanistic insights from epidemiology. *Nat Rev Cancer* 15: 484-498.
40. Baumgartner KB, Hunt WC, Baumgartner RN, et al. (2004) Association of body composition and weight history with breast cancer prognostic markers: divergent pattern for Hispanic and non-Hispanic White women. *Am J Epidemiol* 160: 1087-1097.
41. Harris HR, Willett WC, Terry KL, et al. (2011) Body fat distribution and risk of premenopausal breast cancer in the Nurses' Health Study II. *J Natl Cancer Inst* 103: 273-278.
42. Jiralerspong S, Goodwin PJ (2016) Obesity and Breast Cancer Prognosis: Evidence, Challenges, and Opportunities. *J Clin Oncol* 34: 4203-4216.

43. Arce-Salinas C, Aguilar-Ponce JL, Villarreal-Garza C, et al. (2014) Overweight and obesity as poor prognostic factors in locally advanced breast cancer patients. *Breast Cancer Res Treat* 146: 183-188.
44. Printz C (2014) Obesity associated with higher mortality in women with ER-positive breast cancer. *Cancer* 120: 3267.
45. Ottobelli Chielle E, de Souza WM, da Silva TP, et al. (2016) Adipocytokines, inflammatory and oxidative stress markers of clinical relevance altered in young overweight/obese subjects. *Clin Biochem* 49: 548-553.
46. Bulun SE, Chen D, Moy I, et al. (2012) Aromatase, breast cancer and obesity: a complex interaction. *Trends Endocrinol Metab* 23: 83-89.
47. Creighton CJ, Sada YH, Zhang Y, et al. (2012) A gene transcription signature of obesity in breast cancer. *Breast Cancer Res Treat* 132: 993-1000.
48. Perks CM, Holly JM (2011) Hormonal mechanisms underlying the relationship between obesity and breast cancer. *Endocrinol Metab Clin North Am* 40: 485-507, vii.
49. Vadgama JV, Wu Y, Datta G, et al. (1999) Plasma insulin-like growth factor-I and serum IGF-binding protein 3 can be associated with the progression of breast cancer, and predict the risk of recurrence and the probability of survival in African-American and Hispanic women. *Oncology* 57: 330-340.
50. Kaaks R, Lundin E, Rinaldi S, et al. (2002) Prospective study of IGF-I, IGF-binding proteins, and breast cancer risk, in northern and southern Sweden. *Cancer Causes Control* 13: 307-316.
51. Sugumar A, Liu YC, Xia Q, et al. (2004) Insulin-like growth factor (IGF)-I and IGF-binding protein 3 and the risk of premenopausal breast cancer: a meta-analysis of literature. *Int J Cancer* 111: 293-297.
52. Renehan AG, Harvie M, Howell A (2006) Insulin-like growth factor (IGF)-I, IGF binding protein-3, and breast cancer risk: eight years on. *Endocr Relat Cancer* 13: 273-278.
53. Endogenous H, Breast Cancer Collaborative G, Key TJ, et al. (2010) Insulin-like growth factor 1 (IGF1), IGF binding protein 3 (IGFBP3), and breast cancer risk: pooled individual data analysis of 17 prospective studies. *Lancet Oncol* 11: 530-542.
54. Rinaldi S, Peeters PH, Berrino F, et al. (2006) IGF-I, IGFBP-3 and breast cancer risk in women: The European Prospective Investigation into Cancer and Nutrition (EPIC). *Endocr Relat Cancer* 13: 593-605.
55. Allen NE, Roddam AW, Allen DS, et al. (2005) A prospective study of serum insulin-like growth factor-I (IGF-I), IGF-II, IGF-binding protein-3 and breast cancer risk. *Br J Cancer* 92: 1283-1287.
56. Rinaldi S, Kaaks R, Zeleniuch-Jacquotte A, et al. (2005) Insulin-like growth factor-I, IGF binding protein-3, and breast cancer in young women: a comparison of risk estimates using different peptide assays. *Cancer Epidemiol Biomarkers Prev* 14: 48-52.
57. Schairer C, Hill D, Sturgeon SR, et al. (2004) Serum concentrations of IGF-I, IGFBP-3 and c-peptide and risk of hyperplasia and cancer of the breast in postmenopausal women. *Int J Cancer* 108: 773-779.
58. Signori C, DuBrock C, Richie JP, et al. (2012) Administration of omega-3 fatty acids and Raloxifene to women at high risk of breast cancer: interim feasibility and biomarkers analysis from a clinical trial. *Eur J Clin Nutr* 66: 878-884.
59. Kabat GC, Kim M, Caan BJ, et al. (2009) Repeated measures of serum glucose and insulin in relation to postmenopausal breast cancer. *Int J Cancer* 125: 2704-2710.

60. Goodwin PJ, Ennis M, Pritchard KI, et al. (2012) Insulin- and obesity-related variables in early-stage breast cancer: correlations and time course of prognostic associations. *J Clin Oncol* 30: 164-171.
61. Sun W, Lu J, Wu S, et al. (2016) Association of insulin resistance with breast, ovarian, endometrial and cervical cancers in non-diabetic women. *Am J Cancer Res* 6: 2334-2344.
62. Lee JO, Kim N, Lee HJ, et al. (2016) Resistin, a fat-derived secretory factor, promotes metastasis of MDA-MB-231 human breast cancer cells through ERM activation. *Sci Rep* 6: 18923.
63. Sun CA, Wu MH, Chu CH, et al. (2010) Adipocytokine resistin and breast cancer risk. *Breast Cancer Res Treat* 123: 869-876.
64. Dalamaga M, Sotiropoulos G, Karmaniolas K, et al. (2013) Serum resistin: a biomarker of breast cancer in postmenopausal women? Association with clinicopathological characteristics, tumor markers, inflammatory and metabolic parameters. *Clin Biochem* 46: 584-590.
65. Georgiou GP, Provatopoulou X, Kalogera E, et al. (2016) Serum resistin is inversely related to breast cancer risk in premenopausal women. *Breast* 29: 163-169.
66. Rahbar AR, Nabipour I (2014) The relationship between dietary lipids and serum visfatin and adiponectin levels in postmenopausal women. *Endocr Metab Immune Disord Drug Targets* 14: 84-92.
67. Dalamaga M, Karmaniolas K, Papadavid E, et al. (2011) Elevated serum visfatin/nicotinamide phosphoribosyl-transferase levels are associated with risk of postmenopausal breast cancer independently from adiponectin, leptin, and anthropometric and metabolic parameters. *Menopause* 18: 1198-1204.
68. Lee YC, Yang YH, Su JH, et al. (2011) High visfatin expression in breast cancer tissue is associated with poor survival. *Cancer Epidemiol Biomarkers Prev* 20: 1892-1901.
69. Kim SR, Park HJ, Bae YH, et al. (2012) Curcumin down-regulates visfatin expression and inhibits breast cancer cell invasion. *Endocrinology* 153: 554-563.
70. Li C, Li J, Chen Y, et al. (2016) Effect of curcumin on visfatin and zinc-alpha2-glycoprotein in a rat model of non-alcoholic fatty liver disease. *Acta Cir Bras* 31: 706-713.
71. Gao Y, Wang C, Pan T, et al. (2014) Impact of metformin treatment and swimming exercise on visfatin levels in high-fat-induced obesity rats. *Arq Bras Endocrinol Metabol* 58: 42-47.
72. Maffei M, Halaas J, Ravussin E, et al. (1995) Leptin levels in human and rodent: measurement of plasma leptin and ob RNA in obese and weight-reduced subjects. *Nat Med* 1: 1155-1161.
73. Thompson HJ, Sedlacek SM, Wolfe P, et al. (2015) Impact of Weight Loss on Plasma Leptin and Adiponectin in Overweight-to-Obese Post Menopausal Breast Cancer Survivors. *Nutrients* 7: 5156-5176.
74. Alshaker H, Wang Q, Frampton AE, et al. (2015) Sphingosine kinase 1 contributes to leptin-induced STAT3 phosphorylation through IL-6/gp130 transactivation in oestrogen receptor-negative breast cancer. *Breast Cancer Res Treat* 149: 59-67.
75. Park HS, Park JY, Yu R (2005) Relationship of obesity and visceral adiposity with serum concentrations of CRP, TNF-alpha and IL-6. *Diabetes Res Clin Pract* 69: 29-35.
76. Bowers LW, Brenner AJ, Hursting SD, et al. (2015) Obesity-associated systemic interleukin-6 promotes pre-adipocyte aromatase expression via increased breast cancer cell prostaglandin E2 production. *Breast Cancer Res Treat* 149: 49-57.

77. Imayama I, Ulrich CM, Alfano CM, et al. (2012) Effects of a caloric restriction weight loss diet and exercise on inflammatory biomarkers in overweight/obese postmenopausal women: a randomized controlled trial. *Cancer Res* 72: 2314-2326.
78. Gao D, Rahbar R, Fish EN (2016) CCL5 activation of CCR5 regulates cell metabolism to enhance proliferation of breast cancer cells. *Open Biol* 6.
79. Svensson S, Abrahamsson A, Rodriguez GV, et al. (2015) CCL2 and CCL5 Are Novel Therapeutic Targets for Estrogen-Dependent Breast Cancer. *Clin Cancer Res* 21: 3794-3805.
80. Yaal-Hahoshen N, Shina S, Leider-Trejo L, et al. (2006) The chemokine CCL5 as a potential prognostic factor predicting disease progression in stage II breast cancer patients. *Clin Cancer Res* 12: 4474-4480.
81. D'Esposito V, Liguoro D, Ambrosio MR, et al. (2016) Adipose microenvironment promotes triple negative breast cancer cell invasiveness and dissemination by producing CCL5. *Oncotarget* 7: 24495-24509.
82. Li BH, He FP, Yang X, et al. (2017) Steatosis induced CCL5 contributes to early-stage liver fibrosis in nonalcoholic fatty liver disease progress. *Transl Res* 180: 103-117 e104.
83. Bell LN, Ward JL, Degawa-Yamauchi M, et al. (2006) Adipose tissue production of hepatocyte growth factor contributes to elevated serum HGF in obesity. *Am J Physiol Endocrinol Metab* 291: E843-848.
84. Sundaram S, Freemerman AJ, Johnson AR, et al. (2013) Role of HGF in obesity-associated tumorigenesis: C3(1)-TAg mice as a model for human basal-like breast cancer. *Breast Cancer Res Treat* 142: 489-503.
85. Ristimaki A, Sivula A, Lundin J, et al. (2002) Prognostic significance of elevated cyclooxygenase-2 expression in breast cancer. *Cancer Res* 62: 632-635.
86. Khuder SA, Mutgi AB (2001) Breast cancer and NSAID use: a meta-analysis. *Br J Cancer* 84: 1188-1192.
87. Brown KA, Simpson ER (2012) Obesity and breast cancer: mechanisms and therapeutic implications. *Front Biosci (Elite Ed)* 4: 2515-2524.
88. Davies NJ, Batehup L, Thomas R (2011) The role of diet and physical activity in breast, colorectal, and prostate cancer survivorship: a review of the literature. *Br J Cancer* 105 Suppl 1: S52-73.
89. Cuzick J, Warwick J, Pinney E, et al. (2011) Tamoxifen-induced reduction in mammographic density and breast cancer risk reduction: a nested case-control study. *J Natl Cancer Inst* 103: 744-752.
90. Kaaks R, Bellati C, Venturelli E, et al. (2003) Effects of dietary intervention on IGF-I and IGF-binding proteins, and related alterations in sex steroid metabolism: the Diet and Androgens (DIANA) Randomised Trial. *Eur J Clin Nutr* 57: 1079-1088.
91. Wei M, Brandhorst S, Shelehchi M, et al. (2017) Fasting-mimicking diet and markers/risk factors for aging, diabetes, cancer, and cardiovascular disease. *Sci Transl Med* 9.
92. Sandhu N, Schetter SE, Liao J, et al. (2016) Influence of Obesity on Breast Density Reduction by Omega-3 Fatty Acids: Evidence from a Randomized Clinical Trial. *Cancer Prev Res (Phila)* 9: 275-282.
93. Sanderson M, Peltz G, Perez A, et al. (2010) Diabetes, physical activity and breast cancer among Hispanic women. *Cancer Epidemiol* 34: 556-561.

94. Irwin ML, Varma K, Alvarez-Reeves M, et al. (2009) Randomized controlled trial of aerobic exercise on insulin and insulin-like growth factors in breast cancer survivors: the Yale Exercise and Survivorship study. *Cancer Epidemiol Biomarkers Prev* 18: 306-313.

AIMS Press