The potential contribution of dietary factors to breast cancer prevention

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Breast cancer (BC), the leading cancer in women, is increasing in prevalence worldwide, concurrent with western metabolic epidemics, that is, obesity, metabolic syndrome, and diabetes, and shares major risk factors with these diseases. The corresponding potential for nutritional contributions toward BC prevention is reviewed and related to critical stages in the life cycle and their implications for carcinogenic and pathometabolic trajectories. BC initiation potentially involves diet-related pro-oxidative, inflammatory, and procarcinogenic processes, that interact through combined lipid/fatty acid peroxidation, estrogen metabolism, and related DNA-adduct/depurination/ mutation formation. The pathometabolic trajectory is affected by high estrogen, insulin, and growth factor cascades and resultant accelerated proliferation/ progression. Anthropometric risk factors – high birth weight, adult tallness, adiposity/BMI, and weight gain – are often reflective of these trends. A sex-based nutritional approach targets women's specific risk in western obesogenic environments, associated with increasing fatness, estrogen metabolism, n-6 : n-3 polyunsaturated fatty acid ratio, and n-6 polyunsaturated fatty acid conversion to proinflammatory/ carcinogenic eicosanoids, and effects of timing of life events, for example, ages at menarche, full-term pregnancy, and menopause. Recent large-scale studies have confirmed the effectiveness of the evidence-based recommendations against BC risk, emphasizing low-energy density diets, highly nutritious plant-based regimes, physical activity, and body/abdominal adiposity management. Better understanding of dietary inter-relationships with BC, as applied to food intake, selection, combination, and processing/preparation, and recommended patterns, for example, Mediterranean, DASH, plant-based, low energy density, and low glycemic load, with high nutrient/ phytonutrient density, would increase public motivation and authoritative support for early/timely prevention, optimally merging with other dietary/health goals, for lifelong BC prevention. *European Journal of Cancer Prevention* 26:385–395 Copyright © 2017 The Author(s). Published by Wolters Kluwer Health, Inc.

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Background

Breast cancer (BC) is the most common cancer among women worldwide, with increasing prevalence, particularly the postmenopausal type, and in areas where the incidence had previously been low, such as Japan, China, and southern and eastern Europe (WCRF, AICR, 2007). This epidemiological pattern, which follows those of other western epidemics, and shares similar risk factors – obesity, type 2 diabetes mellitus (T2DM), and cardiovascular disease – strongly suggests that it is part of the pathometabolic prevalence that is closely associated with western lifestyle patterns, and thus may support a nutritional approach to BC prevention.

Among BC cases, only 5–10% were because of genetic defects, with 90–95% attributable to environmental and lifestyle factors – diet and obesity contributing ∼ 30–35 and 10–20%, respectively – providing major opportunities for nutritional prevention (Anand *et al.*, 2008). Among the 5–10% of genetically based BC cases, many were caused by inherited mutations in either the *BRCA1* or the *BRCA2* genes (Anderson and Badzioch, 1993; Blackwood and Weber, 1998), which, according to the number of cohorts, showed a marked increase in penetration over the recent decades, possibly reflecting increased western reproductive and lifestyle risk factors, including western diet, overfatness, smoking, and low physical activity (Friebel *et al.*, 2014; Pettapiece-Phillips *et al.*, 2015).

Critical periods for breast cancer risk and prevention

Early critical periods – before attaining BC protection by cell differentiation through a full-term pregnancy-induced 'molecular signature' (Barton *et al.*, 2014) – are associated with endocrine/metabolic predisposition. Late menarche, early pregnancy/childbearing, and early menopause – all related to reduced number of menstrual cycles, exposure to estrogen, and periods of accelerated cell proliferation, whereas high birth weight (WCRF, AICR, 2007), early menarche, late menopause, and/or no

or late (age > 30 years) childbearing have been shown to increase BC risk (MacMahon, 1993; McPherson *et al.*, 2000; Barton *et al.*, 2014), thus offering opportunities for early nutritional protection (de Boo and Harding, 2006; Swanson *et al.*, 2009).

Whereas overconsumption has been shown to lead to large birth weight (WCRF, AICR, 2007), to early puberty, telarche, and menarche, and to delayed menopause, lower BMI has beneficially delayed puberty and advances the age of menopause (WCRF, AICR, 2007), suggesting that each of these life stages potentially becomes a 'window of risk' – particularly with the western obesogenic diet – or 'a window of opportunity' – for BC prevention by nutritional/lifestyle management (de Waard and Trichopoulos, 1988; Stoll, 1998; Berkey *et al.*, 1999; Shapira, 2001; Colditz *et al.*, 2014).

Endometabolic mechanisms related to breast cancer

Various mechanisms by which diet and lifestyle may promote BC have been reviewed previously (Kaaks, 1996; Vainio and Bianchini, 2002; Lorincz and Sukumar, 2006), suggesting that a sedentary lifestyle, overweight, and a fat-rich diet are associated with insulin resistance and increased androgenic activity, whereas physical activity improves insulin sensitivity and decreases testosterone and insulin-like growth factor 1 (IGF-1) levels. Insulin stimulates the synthesis of androgens in the ovary and the expression of growth hormone receptors, and inhibits liver production of sex hormone-binding globulin and IGF binding proteins 1 and 2, thus increasing the bioavailability of both sex hormones and IGF-1. Postmenopausal overweight is associated with increased peripheral conversion of androgens to estrogens, decreased sex hormone-binding globulin, and increased insulin levels, especially among obese smokers and drinkers (Endogenous Hormones Breast Cancer Collaborative Group *et al.*, 2011), and alcohol intake further increases the synthesis of androgens and estrogens (Rinaldi *et al.*, 2006). Across ages, control of adiposity and dysmetabolism can reduce the risk of aggressive BC subtypes and improve the prognosis (Agresti *et al.*, 2016).

Beyond postmenopausal estrogen sources from adipose tissue aromatization, 27-hydroxycholesterol (27HC) was recently shown to exert an estrogen-like effect, acting as a local endogenous selective estrogen receptor (ER) modulator, which is potentially reduced by anticholesterol drugs and phytonutrients (McDonnell *et al.*, 2014a).

Estrogen's association with BC operates by both hormonal ER-mediated stimulation of breast cell proliferation, with enhanced chances of mutations, and estradiol's genotoxic metabolites that generate oxygen free radicals and alterations, initiating DNA mutagenic processes (Cavalieri and Rogan, 2014); both mechanisms are reduced by a variety of estrogen inhibitors (Santen *et al.*,

2015). High urine DNA adducts in at-risk or active BC cases indicate a critical role for adduct formation in BC initiation and potential use of antioxidants capable of blocking estrogen-DNA-adduct formation and depurination, for example, *N*-acetylcysteine and resveratrol, which have shown inhibitory potential *in vitro* and *in vivo* (Cavalieri and Rogan, 2010).

Sex-based nutrition and female specificity

Women's differential body fat accumulation and distribution, which is increasingly manifested during puberty/adolescence, shows lower abdominal and visceral fat accumulation versus a tendency toward higher gluteal and subcutaneous accumulation than men, and body fat percentage higher than that of men, even with equal BMI; moreover, their lower fat loss on weight-reduction diets, better response to high-protein versus high-carbohydrate diets, higher risks with sedentariness versus greater benefits with exercise, and tendency toward delayed onset of central obesity, metabolic syndrome (MetS), T2DM, cardiovascular disease, and certain cancers – until menopause but accelerated thereafter – together reflect women's differential metabolic and chronological life cycle patterns (Shapira, 2013).

The postmenopausal state causes fat redistribution to an androgenic pattern, with increasing abdominal adiposity and related metabolic risks, including decreased insulin and leptin sensitivities, and changes in glucose and lipid metabolism, resulting in reduced energy expenditure and increased weight gain and obesity, potentially contributing toward the development of BC. This is despite reduced ovarian estrogen secretion, while increasing localized inflammation and estrogen production in breast tissue, and growth factor secretion (Boonyaratanakornkit and Pateetin, 2015).

Together, the above suggests women's need for specific metabolic and chronological perspectives for prevention/intervention, especially against BC, which closely represents the female life cycle pattern as related to endocrine-metabolic and diet-dependent risks (Shapira, 2013).

Recommended lifestyle changes for breast cancer prevention
Lifestyle factors

On the basis of the available evidence (WCRF, AICR, 2007, 2010; Eccles *et al.*, 2013), recommendations from the World Cancer Research Fund and the American Institute for Cancer Research on diet, physical activity, and weight management include the following: (i) maintain adequate body weight; (ii) be physically active; (iii) limit the intake of high-energy density (ED) foods; (iv) eat mostly plant foods; (v) limit the intake of animal foods; (vi) limit alcohol intake; (vii) limit salt and salt-preserved food intake; and (viii) meet nutritional needs through diet; and special recommendations (S1) breast-feed infants exclusively up to 6 months and (S2) after

cancer treatment – follow the recommendations for BC prevention. Associations between each of these recommendations and BC risk (Romaguera et al., 2012; Hastert et al., 2013; Catsburg et al., 2014; Thomson et al., 2014), across tumor subtypes, and considering hormonal receptors and the human epidermal growth factor receptor 2 (HER2) status (Castello et al., 2015), have yielded encouraging results. Accordingly, adherence to only three versus six or more recommendations increased the risk [odds ratio (OR)≈3.00–4.00] for premenopausal and postmenopausal women, respectively.

For postmenopausal women, the three leading recommendations were to eat a plant-based diet, limit high-ED foods, and maintain adequate body weight. Both low-ED and plant-based foods with high fiber and water contents are expected to be more satiating and contribute toward body weight management. Limiting intake of animal foods yielded only a minimal advantage, despite previous recommendations. High sugar intake, particularly in sugar-sweetened beverages (SSB), has shown a direct association with obesity, MetS, and diabetes (Malik et al., 2010; Barrio-Lopez et al., 2013). Alcohol was associated progressively with increased risk (≈35%) for both postmenopausal and premenopausal women. In premenopausal women, 'not limiting high-ED foods' increased almost two-fold the risk of BC, and increased sugar intake predicted earlier age at menarche (Carwile et al., 2015). Correspondingly, lower rates of BC risk (by 16–60%) were found with increased adherence to the World Cancer Research Fund/American Institute for Cancer Research guidelines – which are linked to reduced body fatness and alcohol intake (Hastert et al., 2013; Thomson et al., 2014; Makarem et al., 2015; McKenzie et al., 2015; Kohler et al., 2016) – and with 'adherence to whole grain products' and 'reduced meat and alcohol' (Catsburg et al., 2014). These effects were shown for both ER + and ER − BCs (Hastert et al., 2013; McKenzie et al., 2015) and with increased penetration of BRCA2 (1920–2000) and BC prevalence in the general population, together suggesting that all BC types may potentially benefit from the above preventive measures (Tryggvadottir et al., 2006).

Dietary patterns

Whole food plant-based and low-ED diet: A whole food plant-based diet, which is also tends to be low ED, potentially supports body weight management, and is innately high in micronutrients, including vitamins, minerals, fiber, and phytonutrients, like antioxidants from vegetables, fruits, and whole grains and beans (Assi et al., 2015), which are necessary for enabling proper metabolic patterns. Some of their bioactive compounds – carotenoids, polyphenols, and isothiocyanates – have documented cancer-preventive activity, observed by linear reduction (OR = 0.66) of BC with the 'salad vegetable' pattern in the ORDET study (Sieri et al., 2004), together

explaining how high intake of vegetables and fruits with olive oil (Sieri et al., 2004) has protective potential against BC.

Traditional diets

Some balanced ethnic patterns, such as the Mediterranean diet, were shown to be more easily and successfully translated and applied than the analytical recommendations on the basis of dietary composition, and can thus highly contribute toward dietary prevention of western diseases – including against BC.

Mediterranean diet

The Mediterranean diet pattern is fundamentally plant rich and low ED, providing high amounts of antioxidant flavonoids, carotenoids, and vitamins, plus phytoestrogens, fiber, folate, and a favorable fatty acids (n-3 : n-6) profile (Chlebowski et al., 1986; Berclaz et al., 2004). The DIANA interventional trials showed that Mediterranean dietary principles can reduce body weight, improved fat distribution, reduce insulin levels, and MetS factors, as well as the bioavailability of sex hormones and growth factors (Berrino et al., 2001; Kaaks et al., 2003; Berrino et al., 2005). In a principal component analysis on vegetables, fruit, fish, and legumes, each was associated independently with decreased adjusted risk (OR = 0.67) (Demetriou et al., 2012).

In the recent PREDIMED randomized clinical intervention trial, the multivariable-adjusted hazard ratios versus the control group were lower – 0.32 for the Mediterranean diet with extra-virgin olive oil and 0.59 for the Mediterranean diet with nuts group (Toledo et al., 2015). Even where high-Mediterranean diet adherence did not protect against BC following removal of alcohol intake from the diet score (Schwingshackl and Hoffmann, 2014), it did reduce mortality from other causes (Kim et al., 2011; Izano et al., 2013; de Lorgeril and Salen, 2014).

Okinawan diet

The Okinawan diet, similar to the Mediterranean pattern – very low ED, glycemic load (GL), and fat, while high in fiber, micronutrients, phytochemicals, prebiotic/probiotic, and n-3 polyunsaturated fatty acids (PUFA) – from whole grains, beans, fruits, vegetables, fermented products, and marine foods, eaten fresh/raw or lightly cooked, with limited red meat and n-6 PUFA – has yielded one of the longest-living populations in the world (Tamaki et al., 2015), with many of the traditional foods, herbs, and spices consumed on a regular basis considered 'functional foods' (Willcox et al., 2009). However, local BC mortality has increased concurrently with reduced dietary adherence (Tamaki et al., 2015) and body weight gain of Okinawan women (Tamaki et al., 2014), confirming the effectiveness of the traditional diet and corroborating its structural similarity to the Mediterranean

diet (Willcox *et al.*, 2009; Demetriou *et al.*, 2012), thus highly relevant for BC prevention in other populations as well.

Dietary factors
Beyond general diet characteristics, individual dietary factors can also play an important role either in the development or in the prevention of BC (Rossi *et al.*, 2014), that is, whereas red meat (especially 'well-done'), fat, sugars, and high GL are among the risk factors, whole foods from plant-based and marine sources with high nutrient and phytonutrient density make protective contributions. Some nutrients were shown to exert specific protective effects against the development of BC that are inherently insufficient in the diet, for example, vitamin D (Rossi *et al.*, 2014) and *n*-3 PUFA (Rose, 1993; Simonsen *et al.*, 1998).

Energy density
Limiting the intake of high-ED foods is a well-known strategy to attain higher satiety by lower caloric intake (Ello-Martin *et al.*, 2005). This is because portion size is more closely associated with satiety than its caloric content. Increasing the amounts of fruits and vegetables, starting the meal with a soup or salad and/or with a low-calorie preload, and/or low-fat/low-carbohydrate diets have all been shown to contribute successfully toward reduced caloric intake and better body weight management (Rolls, 2012), and were recently suggested as a leading BC-prevention strategy (WCRF, AICR, 2010; Eccles *et al.*, 2013).

Fat
Despite the previous assumption that dietary fat affects BC, similar to other western diseases – possibly through its contribution to passive overconsumption and resultant overweight and related pathometabolic effects – there is only limited evidence overall suggesting effects on postmenopausal BC (WCRF, AICR, 2007; Khodarahmi and Azadbakht, 2014). Some case–control studies have suggested increased risk of BC with increased fat intake (Thiebaut *et al.*, 2007), whereas this was not observed in most cohort studies (Kim *et al.*, 2006; Lof *et al.*, 2007) or pooled analyses (Smith-Warner *et al.*, 2001).

Saturated fat/fatty acids
The positive association between saturated fatty acids intake and BC risk has been suggested by several case–control and cohort studies, particularly in the etiology of hormone-sensitive rather than receptor-negative BC subtypes (Sieri *et al.*, 2014), and by a meta-analysis of 14 cohort studies (Khodarahmi and Azadbakht, 2014). However, a pooled analysis of eight cohort studies has shown a weak elevation of risk (relative risk = 1.09) with replacement of saturated fatty acids intake by carbohydrate in an isocaloric diet (Smith-Warner *et al.*, 2001).

Monounsaturated fatty acids
An inverse association between monounsaturated fatty acids (MUFA) intake from extra-virgin olive oil and BC risk (Voorrips *et al.*, 2002), as well as its general protective effect (Pelucchi *et al.*, 2011), are attributable to MUFA's innate oxidative stability, improvement of insulin resistance (Farnetti *et al.*, 2011), and to olive oil polyphenols – including hydroxytyrosol and oleuropein aglycone (Menendez *et al.*, 2007) (Fig. 1) – that have shown effective reduction of viability in various human BC cells lines (Owen *et al.*, 2004). However, MUFA intake from hydrogenated fat high in artificial *trans*-fatty acids (as in margarine) was linked to increased risk of BC (Kohlmeier, 1997).

n-3 polyunsaturated fatty acids
Systematic review of cohort studies and meta-analyses showed an inverse association between BC and *n*-3 PUFA and *n*-3 : *n*-6 ratio, especially when confirmed in biological samples, such as adipose tissue, erythrocyte membranes, serum, and plasma (Rose, 1993; Simonsen *et al.*, 1998), possibly because of reduced inflammation, carcinogenic, and oxidative stress and enhanced insulin sensitivity (Larsson *et al.*, 2004), and recently shown reduced obesity trajectory (Simopoulos, 2016). In a cohort of women with early-stage BC, high eicosa-pentaenoic acid and docosahexaenoic acid intakes (>73 mg/day) from foods (marine sources) for 7.3 years reduced BC events by ~25% and modulated BC risk biomarkers – both in premenopausal (Fabian *et al.*, 2015) and in postmenopausal (Hilakivi-Clarke *et al.*, 2002) women – suggesting their potential contribution toward BC prevention.

Fig. 1
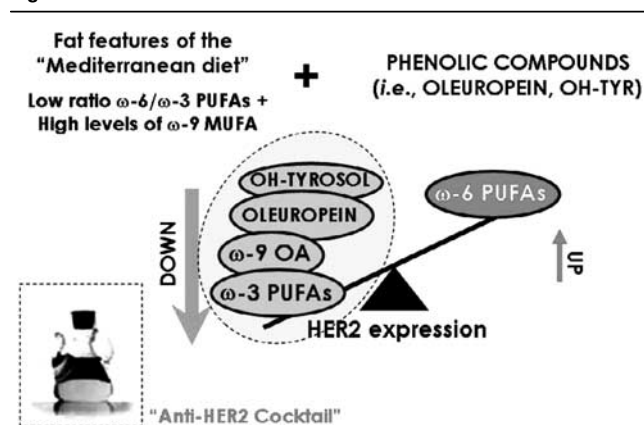
Olive oil as a naturally occurring 'anti-human epidermal growth factor receptor 2 (*HER2*) cocktail'. In terms of protective effects against breast cancer, olive oil has a very favorable fat composition as it appears to combine a new composite biomarker for breast cancer, that is, a low *n*-6 : *n*-3 polyunsaturated fatty acid (PUFA) ratio, and elevated *n*-9 monounsaturated fatty acid (MUFA) levels (Menendez *et al.*, 2007).

n-6 polyunsaturated fatty acids

High intake of *n*-6 PUFA, primarily linoleic acid has been associated with a high prevalence of BC (Shapira, 2012). Increasing *n*-6 : *n*-3 ratio – primarily of long-chain PUFA arachidonic acid (20 : 4) to *n*-3 (eicosapentaenoic acid 20 : 5) in plasma and adipose tissues – was associated with a proinflammatory response, altered adiponectin secretion, and development of MetS (Caspar-Bauguil *et al.*, 2012), enhanced cellular and DNA damage (Wirflät *et al.*, 2002), and accelerated oxidative stress and proinflammatory effects. In contrast, aspirin, the inhibitor of cyclooxygenase 2 – the enzyme that converts long-chain PUFAs into their eicosanoids – was associated in a western high *n*-6 diet with reduced *n*-6 procarcinogenic/proinflammatory compounds (Fig. 2), resulting in improved BC survival and reduced BC and all-cause mortality, as well as with reduced relapse/metastasis when taken before diagnosis (Huang *et al.*, 2015) (although taking after diagnosis was not significantly effective) (Barron *et al.*, 2015).

A biochemical link between estradiol catabolism and *n*-6 PUFA, and resultant lipid oxidation-induced DNA damage (Fig. 3) was shown by in-vivo and in-vitro models (Sun *et al.*, 2012) through enhanced formation of miscoding etheno-DNA adducts (Bartsch *et al.*, 1999) in the white blood cells of women, but not of men (Nair *et al.*, 1997; Bartsch *et al.*, 1999) – with potential for cancer initiation and recurrence (Kiraly *et al.*, 2015) – indicating sex differences and women's greater predisposition with a high *n*-6 diet, very common in the western diet.

The 'Israeli Gender *n*-6 PUFA Nutrition Paradox' hypothesis (Shapira, 2012) links Israeli women's higher disease/cancer risk, relative to men's, with women's inherently greater desaturase activity and *n*-6 PUFA conversion into proinflammatory/oxidative/carcinogenic eicosanoids under conditions of a high *n*-6 diet – compared with men – and resultant worse international health ranking for women.

This further led to Israeli-Jewish women being first in the national cancer over heart disease mortality shift, and to decreasing the gender gap in all diseases and life expectancy, and subsequently to increasing Israeli-Arab women's BC prevalence with *n*-6 consumption, gradually closing the gap towards Jewish women levels (Israel

Fig. 2
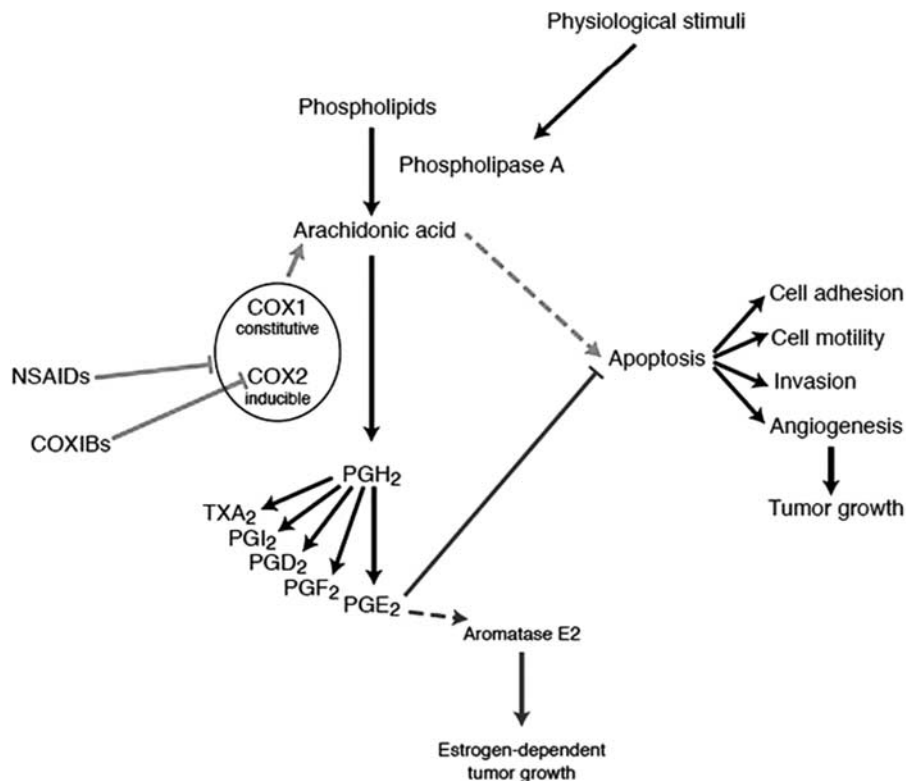
The mechanisms of action of aspirin (anticyclooxygenase products of arachidonic acid). Prostaglandin synthesis through arachidonic acid and the possible effects of cyclooxygenase inhibitors as chemopreventive agents of breast cancer by the intracellular accumulation of arachidonic acid, which directly promotes apoptosis and attenuation of positive feedback for proliferation and survival. COX, cyclooxygenase; COXIBs, COX2 selective inhibitors; PG, prostaglandin; TXA$_2$, thromboxane A$_2$ (Jacobo-Herrera *et al.*, 2014).

Fig. 3
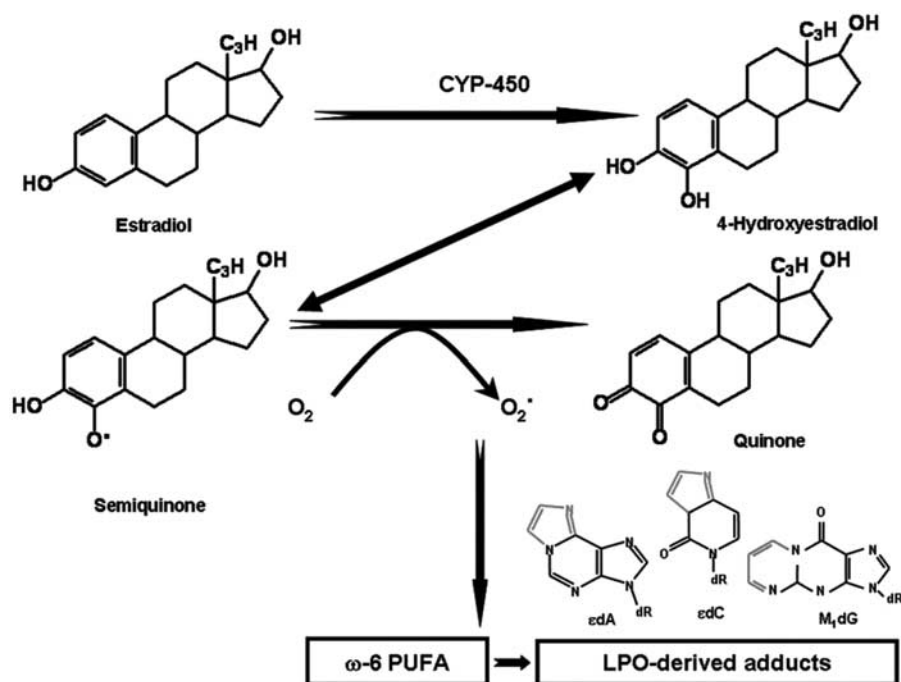
Proposed scheme for metabolic redox-cycling of 4-hydroxyestradiol leading to reactive oxygen species and lipid peroxidation (LPO) of ω-6 polyunsaturated fatty acid (PUFA); the resulting LPO byproducts such as 4-hydroxy-2-nonenal and malondialdehyde generate miscoding etheno-DNA adducts (edA and edC) and M1dG, respectively, that were analyzed in white blood cell of healthy female volunteers (Sun *et al.*, 2012).

National Cancer Registry, 2008). This emphasizes the importance of sex-specific nutrition, especially versus BC.

Cholesterol
Cholesterol was suggested to accelerate and enhance tumor formation, aggression, and angiogenesis, whereas its blood levels are reduced during tumor development (Umetani and Shaul, 2011). A cholesterol metabolite – 27HC – may increase the proliferation of ER + BC cells (Bjarnadottir *et al.*, 2013). The 27HC-producing enzyme, CYP27A1, which is expressed primarily in the liver and in macrophages, was significantly elevated within breast tumors, acting as an ER agonist and stimulating the growth and metastasis of tumors in several models of BC (McDonnell *et al.*, 2014b).

Carbohydrates
Glycemic factors
A prospective cohort analysis (62 739 postmenopausal women, 1812 BC cases) showed no association between dietary carbohydrate or fiber intakes and overall BC risk, but rather an increased risk for BC with glycemic index (GI) among overweight women, and with increased carbohydrate intake, GI, and GL in women with high waist circumference (Lajous *et al.*, 2008). A recent prospective study (European Prospective Investigation into Cancer and Nutrition) reported increased BC risk associated with higher dietary GL, but not GI and total carbohydrate intake (Sieri *et al.*, 2013).

Refined sugars
Frequent consumption of SSB was associated with general and abdominal obesity (Hu and Malik, 2010), MetS (Barrio-Lopez *et al.*, 2013), fatty liver (nonalcoholic fatty liver disease) and T2DM (Malik *et al.*, 2010), and resultant pathometabolic/endocrine outcomes that are related to BC (Basaranoglu *et al.*, 2015). SSB may also reduce the age at menarche, whereas sugar-free (diet) soda and fruit juice consumption was not observed to affect it (Carwile *et al.*, 2015). Fructose – despite a moderate GI – has shown an association with increased lipogenic and proinflammatory effects, and nonalcoholic fatty liver disease (Alwahsh and Gebhardt, 2016). The association between refined sugar and increased risk of BC is further shown by enhanced mammographic breast density with higher intake (Duchaine *et al.*, 2014) and partially explained by its role in increased inflammation and induced 12-LOX signaling in BC development and metastasis (Jiang *et al.*, 2016).

Fiber
Fiber intake has been linked to a reduced risk of BC (by 5% for every additional 10 g/day), potentially by reducing the re-absorption of steroids in the bowel, especially soluble fiber with high absorption capacity, and further

beneficial effects on insulin sensitivity (Aune *et al.*, 2012a). Through gut fermentation, grain fibers (especially from rye) reduce the toxicity of free bile acids and produce short-chain fatty acids such as butyrate, which yield anticancer effects, against BC. Fiber also enhances satiety and reduces the link between alcohol intake and BC risk (Chhim *et al.*, 2015). Lignans and phytic acid from legumes/pulses and whole grains have shown antioxidative and anticarcinogenic potential in general (Norhaizan *et al.*, 2011) and against BC in particular (Adlercreutz, 2010).

Plants and phytonutrients
Vegetables
Total vegetable intake has been related inversely to BC risk, especially legumes/pulses and allium (Bao *et al.*, 2012) and vegetables, particularly cruciferous (Boggs *et al.*, 2010; Suzuki *et al.*, 2013) and raw vegetables (Turati *et al.*, 2015). Broccoli's significant potential is because of the high content of sulforaphane, a potent inducer of detoxification enzymes such as NAD(P)H : quinone oxidoreductase 1 and glutathione-*S*-transferase. NAD(P)H : quinone oxidoreductase 1 and glutathione-*S*-transferase together prevent estrogen–quinone-mediated DNA damage and carcinogenesis (Yang *et al.*, 2013).

High intake of raw vegetables and olive oil showed protection against BC, specifically against *HER2 +* cancers (relative risk = 0.25) as opposed to *HER2 −* cancers (Sant *et al.*, 2007). Vegetables also reduce carbohydrate's glycemic effect, suggesting their protection against BC-related risks of pathological IGF-1 and insulin metabolism (Imai *et al.*, 2014).

Fruits
Although no consistent association has been observed between total fruit intake and BC, high intake of specific fruits, such as citrus and rosaceae, has shown an inverse association (Bao *et al.*, 2012). Beyond their low ED and high nutritional density contributions to satiety, body weight management, and nutritional values, they reduced craving for sweets (Marcinkowski *et al.*, 2012). Fruit antioxidants – especially carotenoids and polyphenols – can reduce the oxidative stress following high GL, preferably eaten as whole rather than fruit juice (Peluso *et al.*, 2014).

Carotenoids
Women with higher circulating levels of α-carotene, β-carotene, lutein + zeaxanthin, lycopene, and total carotenoids may be at reduced risk of BC (Aune *et al.*, 2012b; Eliassen *et al.*, 2012), particularly among smokers and nonusers of dietary supplements (Larsson *et al.*, 2010). In BC cells, carotenoids inhibited IGF-1 induced growth, estrogen-induced proliferation, and further estrogenic activities (Hirsch *et al.*, 2007).

Polyphenols
Table olives are extremely rich in polyphenols (1–3% fresh pulp) (Charoenprasert and Mitchell, 2012) – mostly oleuropein and hydroxytyrosol – all having antioxidative effects, and some also exert antiproliferative effects against human BC cells (Cicerale *et al.*, 2012; Parkinson and Keast, 2014). Peach and plum polyphenols (Vizzotto *et al.*, 2014) have also been shown to reduce BC cell viability and inhibit their proliferation (Vizzotto *et al.*, 2014), and coffee was associated negatively with BC risk of overall and ER + /PR − (Oh *et al.*, 2015). Among polyphenols, carnosic acid, curcumin, silibinin, sulforaphane (Veprik *et al.*, 2012), and punicalagins (from pomegranate) (Shirode *et al.*, 2015) showed reversal of epigenetic alterations and carcinogenesis, including initiation, promotion, and progression (Pan *et al.*, 2015), and some, for example, green tea catechins, showed synergy with certain conventional anti-BC chemotherapy agents such as tamoxifen or raloxifene (Yiannakopoulou, 2014).

Soy isoflavones
Soy isoflavone intake was shown to reduce the risk of BC in both premenopausal and postmenopausal women in Asian countries, although no association was observed for women in western countries for either menopausal status (Chen *et al.*, 2014). Soy isoflavones were also associated with a lower risk of recurrence among postmenopausal patients with BC and individuals receiving endocrine therapy (Guha *et al.*, 2009; Kang *et al.*, 2010), for example, tamoxifen (Guha *et al.*, 2009). A recent meta-analysis summarizing 14 studies further showed that patients who consume moderate amounts of soy throughout their life have a lower BC risk (Dong and Qin, 2011). However , several interventional studies using high doses of soy estrogens have shown changes in breast nipple fluid that would predict higher rates of BC (Willett, 2003). Correspondingly, experts recommend adhering to a moderate intake of isoflavones rather than using their sources as protective foods.

Food processing
Food processing has a significant impact on the total diet effect. Some nutrients may be leached out, whereas others – such as carrot and pepper carotenoids – become more available when cooked in oil, especially olive oil, which increases bioavailability and is itself rich in anti-BC compounds (Agnoli *et al.*, 2015). Conversely, some antioxidants can become pro-oxidants when processed at high temperatures, open heating, grilling, and/or frying. Red meat is especially sensitive to processing, with increasing risk of BC with well-done versus medium rare and low intake among postmenopausal women (Fu *et al.*, 2011).

Summary and conclusion

The present paper presents the multivariate nature of diet association with BC. The most updated support of the potential for BC prevention comes from previous understanding of the endometabolic trajectories under an obesogenic environment, and recent studies showing encouraging results confirming decreased risk across genetic types and menopausal status, through adherence to six to eight basic recommendations, compared with nonadherence. The dietary recommendations include low-ED, low-GL, and nutritious plant-based foods, with minimal intake of animal foods, particularly red/processed meat and alcohol; other lifestyle recommendations include management of physical activity, body/abdominal fatness and adult weight gain, and extended breastfeeding duration.

Nutritional strategies include Mediterranean, DASH, and/or Okinawan patterns, which were found to be more easily applied than the recommendations based on dietary analyses and composition, are especially important during critical risk periods.

Taken together, the existing science supports the potential for lifelong BC prevention, starting from the earliest critical period – *in utero* – throughout the life cycle, with a nutritional approach aiming both for primary prevention of carcinogenesis as well as modification of the metabolic trajectory against disease occurrence and recurrence – to improve survival and quality of life. Increasing incidence of BC, already beyond one out of every eight women, highly necessitates support of the population by health authorities for lifelong BC prevention.

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Conflicts of interest

There are no conflicts of interest.

References

Adlercreutz H (2010). Can rye intake decrease risk of human breast cancer? *Food Nutr Res* 54:5231–5239.

Agnoli C, Grioni S, Sieri S, Sacerdote C, Ricceri F, Tumino R, *et al.* (2015). Metabolic syndrome and breast cancer risk: a case–cohort study nested in a multicentre italian cohort. *PLoS One* 10:e0128891.

Agresti R, Meneghini E, Baili P, Minicozzi P, Turco A, Cavallo I, *et al.* (2016). Association of adiposity, dysmetabolisms, and inflammation with aggressive breast cancer subtypes: a cross-sectional study. *Breast Cancer Res Treat* 157:179–189.

Alwahsh SM, Gebhardt R (2017). Dietary fructose as a risk factor for non-alcoholic fatty liver disease (NAFLD). *Arch Toxicol* 91:1545–1563.

Anand P, Kunnumakkara AB, Sundaram C, Harikumar KB, Tharakan ST, Lai OS, *et al.* (2008). Cancer is a preventable disease that requires major lifestyle changes. *Pharm Res* 25:2097–2116.

Anderson DE, Badzioch MD (1993). Familial breast cancer risks. Effects of prostate and other cancers. *Cancer* 72:114–119.

Assi N, Moskal A, Slimani N, Viallon V, Chajes V, Freisling H, *et al.* (2016). A treelet transform analysis to relate nutrient patterns to the risk of hormonal receptor-defined breast cancer in the European Prospective Investigation into Cancer and Nutrition (EPIC). *Public Health Nutr* 19:242–254.

Aune D, Chan DS, Greenwood DC, Vieira AR, Rosenblatt DA, Vieira R, *et al.* (2012a). Dietary fiber and breast cancer risk: a systematic review and meta-analysis of prospective studies. *Ann Oncol* 23:1394–1402.

Aune D, Chan DS, Vieira AR, Navarro Rosenblatt DA, Vieira R, Greenwood DC, *et al.* (2012b). Dietary compared with blood concentrations of carotenoids and breast cancer risk: a systematic review and meta-analysis of prospective studies. *Am J Clin Nutr* 96:356–373.

Bao PP, Shu XO, Zheng Y, Cai H, Ruan ZX, Gu K, *et al.* (2012). Fruit, vegetable, and animal food intake and breast cancer risk by hormone receptor status. *Nutr Cancer* 64:806–819.

Barrio-Lopez MT, Martinez-Gonzalez MA, Fernandez-Montero A, Beunza JJ, Zazpe I, Bes-Rastrollo M (2013). Prospective study of changes in sugar-sweetened beverage consumption and the incidence of the metabolic syndrome and its components: the SUN cohort. *Br J Nutr* 110:1722–1731.

Barron TI, Murphy LM, Brown C, Bennett K, Visvanathan K, Sharp L (2015). De novo post-diagnosis aspirin use and mortality in women with stage I–III breast cancer. *Cancer Epidemiol Biomarkers Prev* 24:898–904.

Barton M, Santucci-Pereira J, Russo J (2014). Molecular pathways involved in pregnancy-induced prevention against breast cancer. *Front Endocrinol (Lausanne)* 5:213.

Bartsch H, Nair J, Owen RW (1999). Dietary polyunsaturated fatty acids and cancers of the breast and colorectum: emerging evidence for their role as risk modifiers. *Carcinogenesis* 20:2209–2218.

Basaranoglu M, Basaranoglu G, Bugianesi E (2015). Carbohydrate intake and nonalcoholic fatty liver disease: fructose as a weapon of mass destruction. *Hepatobiliary Surg Nutr* 4:109–116.

Berclaz G, Li S, Price KN, Coates AS, Castiglione-Gertsch M, Rudenstam CM, *et al.* (2004). Body mass index as a prognostic feature in operable breast cancer: the International Breast Cancer Study Group experience. *Ann Oncol* 15:875–884.

Berkey CS, Frazier AL, Gardner JD, Colditz GA (1999). Adolescence and breast carcinoma risk. *Cancer* 85:2400–2409.

Berrino F, Bellati C, Secreto G, Camerini E, Pala V, Panico S, *et al.* (2001). Reducing bioavailable sex hormones through a comprehensive change in diet: the s) randomized trial. *Cancer Epidemiol Biomarkers Prev* 10:25–33.

Berrino F, Pasanisi P, Bellati C, Venturelli E, Krogh V, Mastroianni A, *et al.* (2005). Serum testosterone levels and breast cancer recurrence. *Int J Cancer* 113:499–502.

Bjarnadottir O, Romero Q, Bendahl PO, Jirstrom K, Ryden L, Loman N, *et al.* (2013). Targeting HMG-CoA reductase with statins in a window-of-opportunity breast cancer trial. *Breast Cancer Res Treat* 138:499–508.

Blackwood MA, Weber BL (1998). BRCA1 and BRCA2: from molecular genetics to clinical medicine. *J Clin Oncol* 16:1969–1977.

Boggs DA, Palmer JR, Wise LA, Spiegelman D, Stampfer MJ, Adams-Campbell LL, *et al.* (2010). Fruit and vegetable intake in relation to risk of breast cancer in the Black Women's Health Study. *Am J Epidemiol* 172:1268–1279.

Boonyaratanakornkit V, Pateetin P (2015). The role of ovarian sex steroids in metabolic homeostasis, obesity, and postmenopausal breast cancer: molecular mechanisms and therapeutic implications. *BioMed Res Int* 2015: 140196.

Carwile JL, Willett WC, Spiegelman D, Hertzmark E, Rich-Edwards J, Frazier AL, *et al.* (2015). Sugar-sweetened beverage consumption and age at menarche in a prospective study of US girls. *Hum Reprod* 30:675–683.

Caspar-Bauguil S, Fioroni A, Galinier A, Allenbach S, Pujol MC, Salvayre R, *et al.* (2012). Pro-inflammatory phospholipid arachidonic acid/eicosapentaenoic acid ratio of dysmetabolic severely obese women. *Obes Surg* 22:935–944.

Castello A, Martin M, Ruiz A, Casas AM, Baena-Canada JM, Lope V, *et al.* (2015). Lower breast cancer risk among women following the World Cancer Research Fund and American Institute for Cancer Research Lifestyle Recommendations: EpiGEICAM case–control study. *PLoS One* 10: e0126096.

Catsburg C, Miller AB, Rohan TE (2014). Adherence to cancer prevention guidelines and risk of breast cancer. *Int J Cancer* 135:2444–2452.

Cavalieri EL, Rogan EG (2010). Depurinating estrogen-DNA adducts in the etiology and prevention of breast and other human cancers. *Future Oncol* 6:75–91.

Cavalieri E, Rogan E (2014). The molecular etiology and prevention of estrogen-initiated cancers: Ockham's Razor: pluralitas non est ponenda sine necessitate. Plurality should not be posited without necessity. *Mol Aspects Med* 36:1–55.

Charoenprasert S, Mitchell A (2012). Factors influencing phenolic compounds in table olives (*Olea europaea*). *J Agric Food Chem* 60:7081–7095.

Chen M, Rao Y, Zheng Y, Wei S, Li Y, Guo T, *et al.* (2014). Association between soy isoflavone intake and breast cancer risk for pre- and post-menopausal women: a meta-analysis of epidemiological studies. *PLoS One* 9:e89288.

Chhim AS, Fassier P, Latino-Martel P, Druesne-Pecollo N, Zelek L, Duverger L, et al. (2015). Prospective association between alcohol intake and hormone-dependent cancer risk: modulation by dietary fiber intake. Am J Clin Nutr 102:182–189.

Chlebowski RT, Weiner JM, Reynolds R, Luce J, Bulcavage L, Bateman JR (1986). Long-term survival following relapse after 5-FU but not CMF adjuvant breast cancer therapy. Breast Cancer Res Treat 7:23–30.

Cicerale S, Lucas LJ, Keast RSJ (2012). Oleocanthal: a naturally occurring anti-inflammatory agent in virgin olive oil. In: Boskou D, editor. Virgin olive oil, olive oil – constituents, quality, health properties and bioconversions. Rijeka, Croatia: Intech. pp. 357–374.

Colditz GA, Bohlke K, Berkey CS (2014). Breast cancer risk accumulation starts early: prevention must also. Breast Cancer Res Treat 145:567–579.

De Boo HA, Harding JE (2006). The developmental origins of adult disease (Barker) hypothesis. Aust N Z J Obstet Gynaecol 46:4–14.

De Lorgeril M, Salen P (2014). Helping women to good health: breast cancer, omega-3/omega-6 lipids, and related lifestyle factors. BMC Med 12:54.

De Waard F, Trichopoulos D (1988). A unifying concept of the aetiology of breast cancer. Int J Cancer 41:666–669.

Demetriou CA, Hadjisavvas A, Loizidou MA, Loucaides G, Neophytou I, Sieri S, et al. (2012). The Mediterranean dietary pattern and breast cancer risk in Greek-Cypriot women: a case–control study. BMC Cancer 12:113.

Dong JY, Qin LQ (2011). Soy isoflavones consumption and risk of breast cancer incidence or recurrence: a meta-analysis of prospective studies. Breast Cancer Res Treat 125:315–323.

Duchaine CS, Dumas I, Diorio C (2014). Consumption of sweet foods and mammographic breast density: a cross-sectional study. BMC Public Health 14:554.

Eccles SA, Aboagye EO, Ali S, Anderson AS, Armes J, Berditchevski F, et al. (2013). Critical research gaps and translational priorities for the successful prevention and treatment of breast cancer. Breast Cancer Res 15:R92.

Eliassen AH, Hendrickson SJ, Brinton LA, Buring JE, Campos H, Dai Q, et al. (2012). Circulating carotenoids and risk of breast cancer: pooled analysis of eight prospective studies. J Natl Cancer Inst 104:1905–1916.

Ello-Martin JA, Ledikwe JH, Rolls BJ (2005). The influence of food portion size and energy density on energy intake: implications for weight management. Am J Clin Nutr 82 (Suppl):236s–241s.

Key TJ, Appleby PN, Reeves GK, Roddam AW, Helzlsouer KJ, et al., Endogenous Hormones Breast Cancer Collaborative Group (2011). Circulating sex hormones and breast cancer risk factors in postmenopausal women: reanalysis of 13 studies. Br J Cancer 105:709–722.

Fabian CJ, Kimler BF, Phillips TA, Nydegger JL, Kreutzjans AL, Carlson SE, et al. (2015). Modulation of breast cancer risk biomarkers by high-dose omega-3 fatty acids: phase II pilot study in postmenopausal women. Cancer Prev Res (Phila) 8:922–931.

Farnetti S, Malandrino N, Luciani D, Gasbarrini G, Capristo E (2011). Food fried in extra-virgin olive oil improves postprandial insulin response in obese, insulin-resistant women. J Med Food 14:316–321.

Friebel TM, Domchek SM, Rebbeck TR (2014). Modifiers of cancer risk in BRCA1 and BRCA2 mutation carriers: systematic review and meta-analysis. J Natl Cancer Inst 106:dju091.

Fu Z, Deming SL, Fair AM, Shrubsole MJ, Wujcik DM, Shu XO, et al. (2011). Well-done meat intake and meat-derived mutagen exposures in relation to breast cancer risk: the Nashville Breast Health Study. Breast Cancer Res Treat 129:919–928.

Guha N, Kwan ML, Quesenberry CP Jr, Weltzien EK, Castillo AL, Caan BJ (2009). Soy isoflavones and risk of cancer recurrence in a cohort of breast cancer survivors: the Life After Cancer Epidemiology study. Breast Cancer Res Treat 118:395–405.

Hastert TA, Beresford SA, Patterson RE, Kristal AR, White E (2013). Adherence to WCRF/AICR cancer prevention recommendations and risk of postmenopausal breast cancer. Cancer Epidemiol Biomarkers Prev 22:1498–1508.

Hilakivi-Clarke L, Cho E, Cabanes A, deAssis S, Olivo S, Helferich W, et al. (2002). Dietary modulation of pregnancy estrogen levels and breast cancer risk among female rat offspring. Clin Cancer Res 8:3601–3610.

Hirsch K, Atzmon A, Danilenko M, Levy J, Sharoni Y (2007). Lycopene and other carotenoids inhibit estrogenic activity of 17beta-estradiol and genistein in cancer cells. Breast Cancer Res Treat 104:221–230.

Hu FB, Malik VS (2010). Sugar-sweetened beverages and risk of obesity and type 2 diabetes: epidemiologic evidence. Physiol Behav 100:47–54.

Huang XZ, Gao P, Sun JX, Song YX, Tsai CC, Liu J, et al. (2015). Aspirin and nonsteroidal anti-inflammatory drugs after but not before diagnosis are associated with improved breast cancer survival: a meta-analysis. Cancer Causes Control 26:589–600.

Imai S, Fukui M, Kajiyama S (2014). Effect of eating vegetables before carbohydrates on glucose excursions in patients with type 2 diabetes. J Clin Biochem Nutr 54:7–11.

Israel National Cancer Registry (2008). Trends in malignant disease incidence in Israel 1990–2006. Jerusalem, Israel: Israel National Cancer Registry (INCR).

Izano MA, Fung TT, Chiuve SS, Hu FB, Holmes MD (2013). Are diet quality scores after breast cancer diagnosis associated with improved breast cancer survival? Nutr Cancer 65:820–826.

Jacobo-Herrera NJ, Perez-Plasencia C, Camacho-Zavala E, Gonzalez GF, Urrutia EL, Garcia-Castillo V, et al. (2014). Clinical evidence of the relationship between aspirin and breast cancer risk (review). Oncol Rep 32:451.

Jiang Y, Pan Y, Rhea PR, Tan L, Gagea M, Cohen L, et al. (2016). A sucrose-enriched diet promotes tumorigenesis in mammary gland in part through the 12-lipoxygenase pathway. Cancer Res 76:24–29.

Kaaks R (1996). Nutrition, hormones, and breast cancer: is insulin the missing link? Cancer Causes Control 7:605–625.

Kaaks R, Bellati C, Venturelli E, Rinaldi S, Secreto G, Biessy C, 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.

Kang X, Zhang Q, Wang S, Huang X, Jin S (2010). Effect of soy isoflavones on breast cancer recurrence and death for patients receiving adjuvant endocrine therapy. CMAJ 182:1857–1862.

Khodarahmi M, Azadbakht L (2014). The association between different kinds of fat intake and breast cancer risk in women. Int J Prev Med 5:6–15.

Kim EH, Willett WC, Colditz GA, Hankinson SE, Stampfer MJ, Hunter DJ, et al. (2006). Dietary fat and risk of postmenopausal breast cancer in a 20-year follow-up. Am J Epidemiol 164:990–997.

Kim EH, Willett WC, Fung T, Rosner B, Holmes MD (2011). Diet quality indices and postmenopausal breast cancer survival. Nutr Cancer 63:381–388.

Kiraly O, Gong G, Olipitz W, Muthupalani S, Engelward BP (2015). Inflammation-induced cell proliferation potentiates DNA damage-induced mutations in vivo. PLoS Genet 11:e1004901.

Kohler LN, Garcia DO, Harris RB, Oren E, Roe DJ, Jacobs ET (2016). Adherence to diet and physical activity cancer prevention guidelines and cancer outcomes: a systematic review. Cancer Epidemiol Biomarkers Prev 25:1018–1028.

Kohlmeier L (1997). Biomarkers of fatty acid exposure and breast cancer risk. Am J Clin Nutr 66 (Suppl):1548s–1556s.

Lajous M, Boutron-Ruault MC, Fabre A, Clavel-Chapelon F, Romieu I (2008). Carbohydrate intake, glycemic index, glycemic load, and risk of postmenopausal breast cancer in a prospective study of French women. Am J Clin Nutr 87:1384–1391.

Larsson SC, Bergkvist L, Wolk A (2010). Dietary carotenoids and risk of hormone receptor-defined breast cancer in a prospective cohort of Swedish women. Eur J Cancer 46:1079–1085.

Larsson SC, Kumlin M, Ingelman-Sundberg M, Wolk A (2004). Dietary long-chain n-3 fatty acids for the prevention of cancer: a review of potential mechanisms. Am J Clin Nutr 79:935–945.

Lof M, Sandin S, Lagiou P, Hilakivi-Clarke L, Trichopoulos D, Adami HO, et al. (2007). Dietary fat and breast cancer risk in the Swedish women's lifestyle and health cohort. Br J Cancer 97:1570–1576.

Lorincz AM, Sukumar S (2006). Molecular links between obesity and breast cancer. Endocr Relat Cancer 13:279–292.

MacMahon B (1993). General motors cancer research prizewinners laureates lectures. Charles S. Mott Prize. Reproduction and cancer of the breast. Cancer 71:3185–3188.

Makarem N, Lin Y, Bandera EV, Jacques PF, Parekh N (2015). Concordance with World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) guidelines for cancer prevention and obesity-related cancer risk in the Framingham Offspring cohort (1991–2008). Cancer Causes Control 26:277–286.

Malik VS, Popkin BM, Bray GA, Despres JP, Willett WC, Hu FB (2010). Sugar-sweetened beverages and risk of metabolic syndrome and type 2 diabetes: a meta-analysis. Diabetes care 33:2477–2483.

Marcinkowski JT, Edbom-Kolarz A, Bajek A, Wojtyla A, Leppert J, Zagozdzon P, et al. (2012). Comparative studies on promotion of health and life style of hospital staff in Sweden and Poland. Ann Agric Environ Med 19:732–737.

McDonnell DP, Chang CY, Nelson ER (2014a). The estrogen receptor as a mediator of the pathological actions of cholesterol in breast cancer. Climacteric 17 (Suppl 2):60–65.

McDonnell DP, Park S, Goulet MT, Jasper J, Wardell SE, Chang CY, et al. (2014b). Obesity, cholesterol metabolism, and breast cancer pathogenesis. Cancer Res 74:4976–4982.

McKenzie F, Ferrari P, Freisling H, Chajes V, Rinaldi S, de Batlle J, et al. (2015). Healthy lifestyle and risk of breast cancer among postmenopausal women in

the European Prospective Investigation into Cancer and Nutrition cohort study. *Int J Cancer* **136**:2640–2648.

McPherson K, Steel CM, Dixon JM (2000). ABC of breast diseases. Breast cancer-epidemiology, risk factors, and genetics. *Bmj* **321**:624–628.

Menendez JA, Vazquez-Martin A, Colomer R, Brunet J, Carrasco-Pancorbo A, Garcia-Villalba R, *et al.* (2007). Olive oil's bitter principle reverses acquired autoresistance to trastuzumab (Herceptin) in *HER2*-overexpressing breast cancer cells. *BMC Cancer* **7**:80.

Nair J, Vaca CE, Velic I, Mutanen M, Valsta LM, Bartsch H (1997). High dietary omega-6 polyunsaturated fatty acids drastically increase the formation of etheno-DNA base adducts in white blood cells of female subjects. *Cancer Epidemiol Biomarkers Prev* **6**:597–601.

Norhaizan ME, Ng SK, Norashareena MS, Abdah MA (2011). Antioxidant and cytotoxicity effect of rice bran phytic acid as an anticancer agent on ovarian, breast and liver cancer cell lines. *Malays J Nutr* **17**:367–375.

Oh JK, Sandin S, Strom P, Lof M, Adami HO, Weiderpass E (2015). Prospective study of breast cancer in relation to coffee, tea and caffeine in Sweden. *Int J Cancer* **137**:1979–1989.

Owen RW, Haubner R, Wurtele G, Hull E, Spiegelhalder B, Bartsch H (2004). Olives and olive oil in cancer prevention. *Eur J Cancer Prev* **13**:319–326.

Pan MH, Chiou YS, Chen LH, Ho CT (2015). Breast cancer chemoprevention by dietary natural phenolic compounds: specific epigenetic related molecular targets. *Mol Nutr Food Res* **59**:21–35.

Parkinson L, Keast R (2014). Oleocanthal, a phenolic derived from virgin olive oil: a review of the beneficial effects on inflammatory disease. *Int J Mol Sci* **15**:12323–12334.

Pelucchi C, Bosetti C, Negri E, Lipworth L, La Vecchia C (2011). Olive oil and cancer risk: an update of epidemiological findings through 2010. *Curr Pharm Des* **17**:805–812.

Peluso I, Villano DV, Roberts SA, Cesqui E, Raguzzini A, Borges G, *et al.* (2014). Consumption of mixed fruit-juice drink and vitamin C reduces postprandial stress induced by a high fat meal in healthy overweight subjects. *Curr Pharm Des* **20**:1020–1024.

Pettapiece-Phillips R, Narod SA, Kotsopoulos J (2015). The role of body size and physical activity on the risk of breast cancer in BRCA mutation carriers. *Cancer Causes Control* **26**:333–344.

Rinaldi S, Peeters PH, Bezemer ID, Dossus L, Biessy C, Sacerdote C, *et al.* (2006). Relationship of alcohol intake and sex steroid concentrations in blood in pre- and post-menopausal women: the European Prospective Investigation into Cancer and Nutrition. *Cancer Causes Control* **17**:1033–1043.

Rolls BJ (2012). Dietary strategies for weight management. *Nestle Nutr Inst Workshop Ser* **73**:37–48.

Romaguera D, Vergnaud AC, Peeters PH, van Gils CH, Chan DS, Ferrari P, *et al.* (2012). Is concordance with World Cancer Research Fund/American Institute for Cancer Research guidelines for cancer prevention related to subsequent risk of cancer? Results from the EPIC study. *Am J Clin Nutr* **96**:150–163.

Rose DP (1993). Diet, hormones, and cancer. *Annu Rev Public Health* **14**:1–17.

Rossi RE, Pericleous M, Mandair D, Whyand T, Caplin ME (2014). The role of dietary factors in prevention and progression of breast cancer. *Anticancer Res* **34**:6861–6875.

Sant M, Allemani C, Sieri S, Krogh V, Menard S, Tagliabue E, *et al.* (2007). Salad vegetables dietary pattern protects against HER-2-positive breast cancer: a prospective Italian study. *Int J Cancer* **121**:911–914.

Santen RJ, Yue W, Wang JP (2015). Estrogen metabolites and breast cancer. *Steroids* **99** (**Pt A**):61–66.

Schwingshackl L, Hoffmann G (2014). Adherence to Mediterranean diet and risk of cancer: a systematic review and meta-analysis of observational studies. *Int J Cancer* **135**:1884–1897.

Shapira N (2001). Early nutritional prevention of breast cancer: adolescence as a window of opportunity. In: Lebenthal E, Shapira N, editors. *Nutrition in the female life cycle.* Jerusalem, Israel: Danone Institute Israel, ISAS International Seminars Ltd. pp. 176–198.

Shapira N (2012). Women's higher risk with N-6 PUFA vs. men's relative advantage: an '*N*-6 gender nutrition paradox' hypothesis. *Isr Med Assoc J* **14**:435–441.

Shapira N (2013). Women's higher health risks in the obesogenic environment: a gender nutrition approach to metabolic dimorphism with predictive, preventive, and personalised medicine. *EPMA J* **4**:1.

Shirode AB, Bharali DJ, Nallanthighal S, Coon JK, Mousa SA, Reliene R (2015). Nanoencapsulation of pomegranate bioactive compounds for breast cancer chemoprevention. *Int J Nanomedicine* **10**:475–484.

Sieri S, Krogh V, Pala V, Muti P, Micheli A, Evangelista A, *et al.* (2004). Dietary patterns and risk of breast cancer in the ORDET cohort. *Cancer Epidemiol Biomarkers Prev* **13**:567–572.

Sieri S, Pala V, Brighenti F, Agnoli C, Grioni S, Berrino F, *et al.* (2013). High glycemic diet and breast cancer occurrence in the Italian EPIC cohort. *Nutr Metab Cardiovasc Dis* **23**:628–634.

Sieri S, Chiodini P, Agnoli C, Pala V, Berrino F, Trichopoulou A, *et al.* (2014). Dietary fat intake and development of specific breast cancer subtypes. *J Natl Cancer Inst* **106**:pii:dju068.

Simonsen N, van't Veer P, Strain JJ, Martin-Moreno JM, Huttunen JK, Navajas JF, *et al.* (1998). Adipose tissue omega-3 and omega-6 fatty acid content and breast cancer in the EURAMIC study. European Community Multicenter Study on Antioxidants, Myocardial Infarction, and Breast Cancer. *Am J Epidemiol* **147**:342–352.

Simopoulos AP (2016). An increase in the omega-6/omega-3 fatty acid ratio increases the risk for obesity. *Nutrients* **8**:128.

Smith-Warner SA, Spiegelman D, Adami HO, Beeson WL, van den Brandt PA, Folsom AR, *et al.* (2001). Types of dietary fat and breast cancer: a pooled analysis of cohort studies. *Int J Cancer* **92**:767–774.

Stoll BA (1998). Western diet, early puberty, and breast cancer risk. *Breast Cancer Res Treat* **49**:187–193.

Sun X, Nair J, Linseisen J, Owen RW, Bartsch H (2012). Lipid peroxidation and DNA adduct formation in lymphocytes of premenopausal women: role of estrogen metabolites and fatty acid intake. *Int J Cancer* **131**: 1983–1990.

Suzuki R, Iwasaki M, Hara A, Inoue M, Sasazuki S, Sawada N, *et al.* (2013). Fruit and vegetable intake and breast cancer risk defined by estrogen and pro-gesterone receptor status: the Japan Public Health Center-based Prospective Study. *Cancer Causes Control* **24**:2117–2128.

Swanson JM, Entringer S, Buss C, Wadhwa PD (2009). Developmental origins of health and disease: environmental exposures. *Semin Reprod Med* **27**:391–402.

Tamaki K, Tamaki N, Terukina S, Kamada Y, Uehara K, Arakaki M, *et al.* (2014). The correlation between body mass index and breast cancer risk or estrogen receptor status in Okinawan women. *Tohoku J Exp Med* **234**:169–174.

Tamaki K, Tamaki N, Kamada Y, Uehara K, Zaha H, Onomura M, *et al.* (2015). Can we improve breast cancer mortality in Okinawa? Consensus of the 7th Okinawa Breast Oncology Meeting. *Tohoku J Exp Med* **235**:111–115.

Thiebaut AC, Kipnis V, Chang SC, Subar AF, Thompson FE, Rosenberg PS, *et al.* (2007). Dietary fat and postmenopausal invasive breast cancer in the National Institutes of Health-AARP Diet and Health Study cohort. *J Natl Cancer Inst* **99**:451–462.

Thomson CA, McCullough ML, Wertheim BC, Chlebowski RT, Martinez ME, Stefanick ML, *et al.* (2014). Nutrition and physical activity cancer prevention guidelines, cancer risk, and mortality in the women's health initiative. *Cancer Prev Res (Phila)* **7**:42–53.

Toledo E, Salas-Salvado J, Donat-Vargas C, Buil-Cosiales P, Estruch R, Ros E, *et al.* (2015). Mediterranean diet and invasive breast cancer risk among women at high risk in the PREDIMED Trial: a randomized clinical trial. *JAMA Intern Med* **175**:1752–1760.

Tryggvadottir L, Sigvaldason H, Olafsdottir GH, Jonasson JG, Jonsson T, Tulinius H, *et al.* (2006). Population-based study of changing breast cancer risk in Icelandic *BRCA2* mutation carriers, 1920–2000. *J Natl Cancer Inst* **98**:116–122.

Turati F, Rossi M, Pelucchi C, Levi F, La Vecchia C (2015). Fruit and vegetables and cancer risk: a review of southern European studies. *Br J Nutr* **113** (Suppl 2):S102–S110.

Umetani M, Shaul PW (2011). 27-Hydroxycholesterol: the first identified endogenous SERM. *Trends Endocrinol Metab* **22**:130–135.

Vainio H, Bianchini F (2002). *Weight control and physical activity*. Lyon, France: IARC Handbooks of Cancer Prevention.

Veprik A, Khanin M, Linnewiel-Hermoni K, Danilenko M, Levy J, Sharoni Y (2012). Polyphenols, isothiocyanates, and carotenoid derivatives enhance estrogenic activity in bone cells but inhibit it in breast cancer cells. *Am J Physiol Endocrinol Metab* **303**:E815–E824.

Vizzotto M, Porter W, Byrne D, Cisneros-Zevallos L (2014). Polyphenols of selected peach and plum genotypes reduce cell viability and inhibit pro-liferation of breast cancer cells while not affecting normal cells. *Food Chem* **164**:363–370.

Voorrips LE, Brants HA, Kardinaal AF, Hiddink GJ, van den Brandt PA, Goldbohm RA (2002). Intake of conjugated linoleic acid, fat, and other fatty acids in relation to postmenopausal breast cancer: the Netherlands Cohort Study on Diet and Cancer. *Am J Clin Nutr* **76**:873–882.

WCRF, AICR. WCRF AICR (2007). Breast cancer. *Food, nutrition, physical activity, and the prevention of cancer: a global perspective.* Washington, DC: American Institute for Cancer Research. pp. 289–295.

WCRF, AICR. WCRF AICR (2010). Continuous update project report. *Food, nutrition, physical activity, and the prevention of breast cancer*. Washington, DC: American Institute for Cancer Research.

Willcox DC, Willcox BJ, Todoriki H, Suzuki M (2009). The Okinawan diet: health implications of a low-calorie, nutrient-dense, antioxidant-rich dietary pattern low in glycemic load. *J Am Coll Nutr* **28** (Suppl): 500s–516s.

Willett W (2003). Lessons from dietary studies in Adventists and questions for the future. *Am J Clin Nutr* **78** (Suppl):539s–543s.

Wirfalt E, Mattisson I, Gullberg B, Johansson U, Olsson H, Berglund G (2002). Postmenopausal breast cancer is associated with high intakes of omega6 fatty acids (Sweden). *Cancer Causes Control* **13**:883–893.

Yang L, Zahid M, Liao Y, Rogan EG, Cavalieri EL, Davidson NE, *et al.* (2013). Reduced formation of depurinating estrogen-DNA adducts by sulforaphane or KEAP1 disruption in human mammary epithelial MCF-10A cells. *Carcinogenesis* **34**:2587–2592.

Yiannakopoulou EC (2014). Interaction of green tea catechins with breast cancer endocrine treatment: a systematic review. *Pharmacology* **94**:245–248.