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Review

Hormonal and metabolic modulation through nutrition: Towards a primary prevention of breast cancer

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ABSTRACT

Breast cancer (BC) is a polygenic and multifactorial disease for which estrogens have been recognized as the main risk factor, and for which lifestyle plays a key role. Previous epidemiologic cancer research performed in Uruguayan population delimited its dietary and anthropometric profiles. Recognizing the difficulty for universalizing a nutritional basis for prevention due to different eating patterns among regions and countries, we summarize the existent knowledge linking nutrition, estrogens, metabolism and BC. As an attempt towards primary prevention of BC, we present recommendations mainly based on country-specific research findings and modifiable putative risk and protective factors, proposing to modify the intake of meats and other fatty foods – especially sources of Ω-6 and Ω-3 fatty acids – adding olive oil, selected vegetables, citrus fruits and working towards adequate body fat/muscle proportions. From a medical and ethical viewpoint, it is justified to recommend certain nutritional changes to women, because no adverse side effects are expected to occur.

Introduction

Although breast cancer (BC) is still a major public health issue in developed societies, its incidence has been rising in several developing countries over the past few years. International data[1] have located Uruguay among those with the highest rates in the world. Moreover, the capital city, Montevideo, has displayed the highest incidence rate for a city.[2] In fact, although this small South American country is a developing one, it shares some characteristics with developed regions, i.e. a very high level of red meat consumption,[3] a high human development index (50° in the world ranking according to United Nations, by factors as birth rate, infant mortality, life expectancy, literacy among others)[4] and an aged population.[5] In other words, a developing country has shown a high occurrence of a disease typical of developed countries. The top-ranking BC incident areas[1] are North America, a large part of the European Union, Australia, New Zealand, Israel, and in Latin America only two exceptions: Uruguay and Argentina. The incidence ranking of the last years has notably changed, due to the rise in some countries belonging to the former Soviet Union, and some other undeveloped ones.[1] The fact that the above quoted countries are cattle producers and high meat consumers might not be a coincidence: Uruguay is the country with the highest beef per capita intake in the world.[6]

Being a developed country is not mandatory for being in a high-risk situation: Japan, for example, has lower rates than the quoted countries from Northern hemisphere. Conversely, cancer registries in Uruguay, Argentina and Southern Brazil have shown higher rates in the region than in the rest of the Latin American developing countries. While the urbanization process continues, educational levels increase and people change their habits, as a result of which the occurrence of BC increases. This is not due to only one of these factors, but is an outcome of several of them combined. Higher educational levels correspond to a reduction in the average number of pregnancies and births, an increase of age at the first birth, as well as reduced times of breastfeeding. Urbanization implies an increase in job types that are less active than rural ones, this being favorable for the development of problems such as excess weight and obesity. Outdoor jobs performed by women, regardless of the conditions under which they are performed, are associated with high caloric- and fast-foods, as well as psychosocial stress.

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The most severely affected women from developing countries are those who belong to the mid-to-high socioeconomic and cultural classes and who accumulate menstrual and reproductive risk factors with some environmental ones. Because of these socioeconomic and environmental factors, these women belong to a "first world" within the third world. The situation is not the same in all these countries, nevertheless. In Uruguay, Argentina and Southern Brazil there is a high consumption of red meat, cooked by direct heat, like barbecue, beefsteak, hamburgers and fried meat. In this region of the world, meat is the axis of the daily meal and it is cheaper than in the Northern hemisphere. Average salaries are lower but so are the prices of meat. It is obvious then why women of low social strata in other Latin American countries, conversely, have not got such high BC rates: while they display protective reproductive factors, their dietary profiles have a higher proportion of plant foods, and meat is not so accessible due to its high price. In our opinion, the "first world" situation can also be applied to a small section of the Uruguayan society: as an example, the coastal strip of mid-to-high residential neighborhoods in Montevideo has a twice higher incidence than the rest of the city, according to a study from 2002.[7]

We and others have thoroughly studied possible links of nutrition and BC, from the dietary viewpoint[8–20] as well as from an anthropometric one.[21,22] Uruguay has been recognized as the Latin American country with more specialized studies on diet and BC.[23] The main objective of this analysis is to consider, within realistic terms, the current background to support the idea of a primary prevention of BC that could be expected to take place in a near future. Our work is not focused only on pure theoretical basis of the problem, but we also attempt to improve the probabilities of facing it from a practical viewpoint.

Recognition of the problem

Estrogens were recognized five decades ago as the main risk factor for developing BC.[24] However, their assessment has been relatively limited to a "traditional" exposure analysis that is, based on menstrual and reproductive factors and family history. Currently, the importance of other risk factors different from such classic ones is somehow underestimated. Nevertheless, it is a positive fact to recognize that BC is an essentially preventable tumor, through the different ways that prevention can be developed. Primary prevention attempts to reduce incidence through a reduction in the exposure to risk factors and/or through an increase in exposure to protective factors.

The attributable risks related to BC can be summarized as follows: A responsibility of 5% and no more than 15% of all cases is recognized for the family history of cancer. A high-risk family history, based on certain demonstrated gene mutations, accounts for between 2 and 5% of all cases. Menstrual and reproductive factors (early menarche, nulliparity, late first delivery, short breastfeeding time, late menopause, as major factors) are thought to account for 25% of the cases of BC. Considered together, these classic factors explain between 30 and 40% of the incidence. The rest are mostly environmental modifiable factors, and they correspond to a 60–70%. Of these, diet is considered the most important one. It is accepted that a risk reduction through influencing dietary factors can reach a 30–35% of the whole risk. The rest of factors include excess weight and obesity, metabolic factors (i.e. insulin resistance, low serum vitamin D level, dislypidemia, diabetes), sedentariness or low level of physical activity and psychosocial stress among other possible factors.

An experimental study from 1942 found a higher incidence of BC in rats fed with a fat-rich diet.[25] Over time, this concept has been changing and expanding. Then some of the most powerful indicators relating diet to the etiology of BC emerged from ecologic and migrant studies. In fact, the latter showed that migrants acquired the cancer patterns of the host countries within some given time periods, hence, they constituted a support to the hypothesis that primary prevention of BC could be a realistic option. Several studies on migrants reported that BC incidence could not be substantially changed for first-generation immigrants, though this was possible for the second and third generations.[26] Such delay would indicate a stronger influence of lifestyle factors – i.e. diet – during childhood on the risk of BC, and it would agree to the existence of a long latency period for the disease during which carcinogen factors (known or unknown) would exert their deleterious action. Studies on migrants in Uruguay revealed a risk increase for the foreign residents in the country compared to that of their home countries, Spain and Italy[27] and an older mean age for cancer mortality in foreign women compared to Uruguayan ones.[28] These studies agreed with the existing literature.

Specialized scientific literature from 1997[29] stated that dietary aspects and their relationship with BC were still not well established, except for a few factors. Moreover, recent opinions of an expert panel confirmed the aforementioned concepts.[30] The international experts have usually made general recommendations, promoting a reduced intake of red meats replacing them with white meats, and a frequent intake of vegetables and fruits. This can be easy to understand for everybody and supposes a minimal strategy of primary prevention.

A considerable limitation derived from the information proceeding from specialized scientific studies, however, is that they come mostly from developed countries (i.e. North America, European Union), which is acceptable because they are countries with high incidence of the disease. But environmental factors – including diet – are not the same in the developing world than in the developed one. Ethnicity also differs within the local or regional factors, and this can influence the process. All that information is not always applicable in the case of developing countries. There are some aspects that have reached a universal status (as menstrual and reproductive factors), but nutrition has not. Genomic research has been weakening the existent paradigm of the "average subjects", leading to a new vision of constitutive differences among individuals.

From a nutritional perspective, cancers are associated mostly to excesses or defects. Excesses are represented by typical dietary patterns in the Rio de la Plata (Uruguay, Argentina) and Southern Brazilian regions, since they have high meat consumption (several dozens of kilograms per capita per year) with an excessive caloric intake based on certain fats and refined sugars. Defects also characterize these countries, since they are recognized as populations with low intake of fish, vegetables and fruits. The resulting imbalance of such excesses and defects enhance some susceptible organisms to create the proper environment to initiate and develop carcinogenesis.

Based on what we have described, the knowledge has routed towards multifactoriality: elements at different levels (biological, socio-cultural, environmental) of a woman interact during years, because of which in certain given conditions a BC will be initiated and promoted. There is currently enough epidemiologic, clinical and experimental evidence to state that BC is a complex hormonal, metabolic and immune problem. However, since estrogens have already been recognized as the main risk factor for developing BC, it seems that most factors converge towards an inadequate exposure to some of them during an inadequate time period.

Previous knowledge on classic risk factors (menstrual-reproductive history and family history) has led to the idea that women who have been exposed for a longer time period or more intensely to endogenous estrogens will have an increased risk of BC. However, scientific research has demonstrated that diet, fat excess and a low level of physical activity can also strongly affect the hormonal production and availability,[31,32] independently from

having or not any of the quoted "classic" risk factors. The ultimate goal of the strategy should be to achieve a hormonal and metabolic modulation through nutritional factors, which are the ones playing a major role within lifestyle.

The good and bad estrogens

The estrogens issue is not restricted only to what has been said. It is, in fact, a problem of excess of estrogenic "capital". This excessive amount conditions the nourishment of the mammary tissue in such a way that it generates a dependence of this tissue on the estrogens. After some estrogens (estradiol and estrone) are synthesized their life follows one of 2 possible pathways leading to catechol hormones: they can derive into very active metabolites, the 16- and 4-α-hydroxyestrogens (the "bad" ones), or they can form low active compounds, the 2α-hydroxyestrogens (the "good" ones).[33] Cells have a structure, the phase I enzyme cytochrome P-450 (CYP450), a kind of metabolic switch which depending on its state derives the production of metabolites towards one or the other.[34] The initial findings have led other authors to develop a theory, which has been supported by newer findings.[35–37]

The "bad" estrogens are believed to participate in the initiation process (they are genotoxic) as well in the promotion (enhancing cell proliferation). Altogether, having a dual role as substrate for phase I enzymes CYP450 (CYP 1A1 and 1B1) and as ligands for estrogen receptors they promote events that increase the risk of BC. Furthermore, such enzymes oxidize catechol estrogens to semi-quinones and quinones, substances which have been recognized as having common features of many chemical carcinogens.[38,39] In particular 3,4-quinones were recently postulated as a possible independent risk factor.[40] It has also been postulated that the genotoxicity caused by the oxidative metabolism of estrogens can be decreased by reactions of metabolites with phase II enzymes, like catechol-o-methyl-transferase (COMT)[41] and glutathione S-transferase P1 (GSTP1).[42] Women who metabolize a large proportion of their estrogens via the 16α hydroxylation pathway could be at a higher risk of BC.[43] Women with cancer, besides, have an increased production of "bad" estrogens (16- and 4-αOH metabolites), but healthy women produce them constantly. Interestingly, the main conversion to 4-αOH estrogens has been detected in uterine myometrium and benign myomas[44] and in benign and malignant mammary tumors.[45] The 16-αOH metabolites have a higher affinity for the estrogen receptor (ER) than the 2-αOH metabolites, while these latter may inhibit angiogenesis.[46]

A recent study suggested that the ratio of 2/16-αOH metabolites may be a marker for lifestyle influences on estrogen metabolism associated with westernization.[47] In addition, Parl et al.[40], having recognized that each of the phase I and II enzymes contains genetic polymorphisms,[48,49] proposed that it could be possible to develop more refined predictive models by integrating known reproductive and lifestyle factors with predicted exposure to estrogen-3,4 quinones —determined by inherited variations in genes involved in estrogen metabolism—. On the contrary, "good" estrogens are also weakly anti-estrogenic. The group of "good" estrogens is the one which can be modified. Items associated with the synthesis of 2-αOHestrogens are the following.[50,51]

a) Factors which increase BC risk by reducing the 2/16-αOH estrogens ratio: sedentariness, heritage, obesity, high-fat diet, human papilloma virus, dimethylbenzanthracene, polycyclic aromatic amines and high intake of Ω-6 fatty acids
b) Factors which reduce BC risk by increasing the 2/16-αOH estrogens ratio: physical exercise, muscularity, slenderness (low BMI), oil fish, cruciferous vegetables, indole-3-carbinol, diindolylmethane, high intake of Ω-3 fatty acids

Estrogen synthesis takes place not only in the ovaries: in particular after menopause, the suprarenal glands and adipocytes are major sources. If body fat is excessive there is an increased hormonal bioavailability. In addition, in the adipose tissue androgens which are gathered from the circulation are also transformed into estrogens through the action of the aromatase (also an enzyme of CYP450), in the process known as "androgen aromatization". Modern hormone therapy is attempting to inhibit this process with drugs such as letrozol or anastrozol. In addition, obesity creates a doubly favorable environment for mammary carcinogenesis, since insulin requirements and androgen aromatization are stimulated and increased, the latter for producing more estrogens. Aromatization is stimulated bearing an excessive adipose mass, especially in the thighs, buttocks and abdominal-pelvic regions (gynoid obesity), with a high intake of Ω-6 polyunsaturated fatty acids (PUFAs) and having increased circulating glucocorticoids[52] (produced under stress, also administered to treat inflammatory processes). Women would require supplemental Indole-3-Carbinol (I3C) at 300–400 mg/day to significantly increase the 2/16-αOHestrogens ratio.[53] Animal studies showed that it is not I3C but diindolylmethane the active promoter of greater 2-hydroxylation of estrogen associated with a cancer-resistant estrogen metabolism.[50]

As it can be seen, the main problem for women is more complex than simply being highly exposed to hormones. The point is to be exposed to high levels of some of them in particular, in addition to the exposure time. It is an accumulative effect, in the sense of amount × time. Excessive and/or "bad" estrogens bind their corresponding receptors in those cells where they must take action and generate a cascade of molecular events which after years of influence might increase the risk of developing a cancer. Furthermore, when there is an excess of estrogen, although it is eliminated through the bile duct to the intestines, part of it is captured by the liver and returns to the blood system—the process known as enterohepatic circulation—and becomes available once again. The aforementioned situation is even more intense when women are afflicted by slow intestinal transit: the more the stools remain in the large bowel, the higher the opportunity of being reabsorbed and reutilized. Women should reassure themselves that what seems to be eliminated is actually eliminated. Among other reasons, the latter is useful to recognize the benefits of an adequate fiber intake derived from eating fruits and vegetables.

In a publication from the last decade,[13] we showed that food intake was a better discriminant between the BC cases and healthy controls, when compared with other variable groups (menstrual-reproductive, family history of cancer, sociodemographics). Hence, the nutritional profile might be playing some role despite the fact that we do not know exactly which it is. This can be one way of contributing to defining a risk population, through their nutritional profile.

In view of the preceding arguments, it could be more understandable why Uruguayan women belonging to the lowest socio-economic classes —also usually having a more favorable menstrual-reproductive history (several births beginning at early ages, long periods of breastfeeding, etc)— could also be prone to developing cancer: they tend to be overweight or obese, have a sedentary lifestyle and display dietary patterns which are more typical of Western developed societies. Should their reproductive history be protective, it seems insufficient to antagonize their environmental/lifestyle risk factors.

The following scheme (Fig. 1) details the probable implications of the current Western nutritional style and its derived consequences, which we have already described for Uruguayan women.[54] In the central picture two key elements appear: excessive dietary cholesterol and an inadequate Ω-6/Ω-3 PUFA ratio. The long chain of metabolic and hormonal events resulting from these

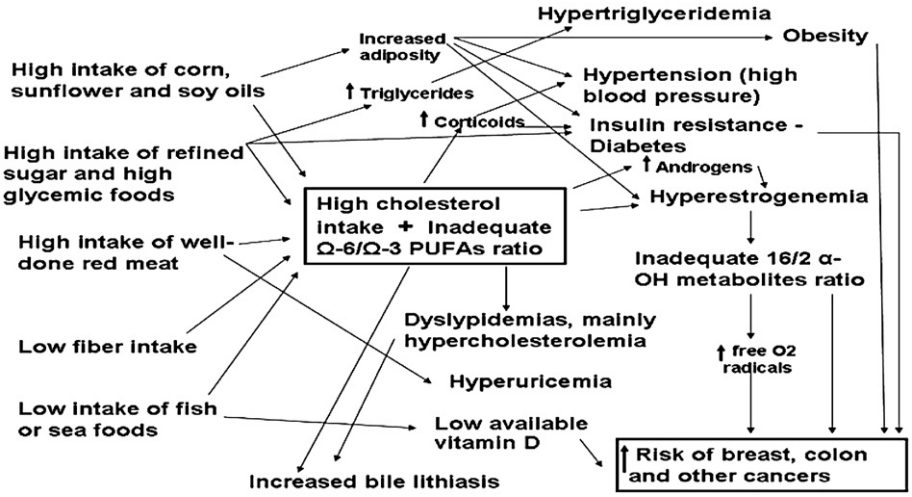

Fig. 1. Possible consequences of a Western diet.

two excesses can finally facilitate the beginning and development of several cancers, among them BC, as well as several pathologic states involved in the metabolic syndrome.

Although the literature suggests that high-fat diets can increase the risk of the disease and there are acceptable mechanisms with biological plausibility, there has been some inconsistency in terms of results.[29,30] On this basis, but at the same time attempting to somehow clarify the influence of nutritional elements on the origin of BC (which can be mostly modifiable), apparently healthy women could be encouraged to try some changes in their diet and lifestyle. These are the challenges of a primary prevention.

Dietary basis

It has been suggested that diet is an important determinant of cancer.[55] In fact, expert reviews have shown that the risk of BC varies with diet.[30] Nevertheless, people eat different foods containing several combinations of nutrients and non-nutrients. It is often difficult, therefore, to identify a single nutrient or food item as related to the risk of a disease. As a consequence, the analysis of individual nutrients, food items, or food groups may result in missing an association between diet and disease.

Foods and food groups

Vegetables

Experimental research has demonstrated that the inclusion of different vegetables in the diet of rats was followed of a lower incidence of induced mammary tumors.[56,57] Although studies in Italian[58] and German[59] women also found protective effects for it, vegetable consumption and the risk of BC have been examined by expert panels, suggesting that there is still limited evidence and they can not be conclusive about this.[30]

In Uruguay, the highest quartiles of total vegetable consumption (OR = 0.41, 95% CI 0.26–0.65), green leaf vegetables (OR = 0.36, 95% CI 0.23–0.55) and raw vegetables (OR = 0.51, 95% CI 0.33–0.79) as well as cooked ones (RR = 0.58, 95% CI 0.36–0.94) were inversely associated with the risk of BC.[12] Also the highest consumers of vegetable-derived fiber[11] displayed a significant negative association (OR = 0.56, 95% CI 0.34–0.92, p for trend = 0.005). On the contrary, cruciferous vegetables did not display an association.[12] We found two protective dietary patterns[18]: A factor labeled as "traditional", which loaded high for boiled meat, grains, cooked vegetables and tubers (OR for high intake = 0.53, 95% CI 0.35–0.79), and a factor labeled as "healthy", featured by high loadings of white meat, raw vegetables, cooked vegetables and total fruits (OR = 0.46, 95% CI 0.31–0.69). More recently, a multisite study performed in Uruguay displayed a protective effect for the highest consumers of vegetables and fruits combined (OR = 0.47, 95% CI: 0.31–0.71).[60]

Fruits

Some studies that examined fruit consumption have communicated null associations[61,62] and a risk reduction in the highest intake levels[63,64] or risk increase for low intake.[65] A case-control study carried out at Uruguayan public hospitals,[12] which focused on plant foods and their nutrients showed a negative association with high intake of total fruits (OR = 0.57, 95% CI 0.36–0.89). Another study performed in the Uruguayan prepaid healthcare system focused especially on fruits consumption.[20] The main findings of this study were a significant protective effect observed in the highest tertiles of total fruits (OR = 0.44, 95% CI 0.23–0.86), oranges (OR = 0.51, 95% CI 0.26–0.98), orange juice (OR = 0.26, 95% CI 0.13–0.54) and citrus fruits (OR = 0.27, 95% CI 0.13–0.55). On the other hand, negative but not significant associations were found for green apples (Granny Smith type) with a borderline (OR = 0.55, 95% CI 0.31–1.01) and plums (OR = 0.62, 95% CI 0.34–1.11). Besides, when a term for vitamin C was included in the regression model, the protective effect was improved in all of them, in particular in orange intake (OR = 0.22, 95% CI 0.08–0.64) and citrus fruits (OR = 0.13, 95% CI 0.05–0.33), suggesting a possible co-responsibility of other substances, as flavonoids. Diets rich in vegetables and fruits probably reduce the risk of BC, according to the existing literature.[66] The intake of vitamin C among Uruguayan women derived from citrus intake suggests a protective effect within their dietary patterns. Besides, the highest consumers of fruit-derived fiber[11] displayed no association (OR = 0.77, 95% CI 0.48–1.24). The potential biologic mechanisms through which the vitamin could protect against BC involve its roles as antioxidant, as well as those in the protein synthesis of conjunctive tissue and in immunologic surveillance. Furthermore, a low intake could increase the risk, which would be related to a reduction in telomere length.[67]

Legumes

Our studies in Uruguay showed different results regarding the associations between legumes intake and the risk of BC: The highest vs. the lowest quartile displayed a significant (OR = 0.42, 95% CI 0.26–0.66)[12] and an also significant OR = 0.53 (95% CI 0.35–0.81),[14] both with a significant trend (p = 0.004). The legumes

included in our questionnaires were: lentils, beans, common peas and garbanzo peas. A recent study on legumes and cancer risk,[68] whose data were extracted from lentils and beans, found no association for high legume consumers and BC risk (OR = 0.89, 95% CI 0.65–1.20). The evidence linking legumes and the risk of BC is limited, but they could be protective.

Red meat

The evaluation of meat as a risk factor for BC was initially focused on its role as a source of dietary fat or animal protein. However, the study by Toniolo et al.[69]found that meat intake but not of total fat or protein increased the risk of BC significantly.

One of the Uruguayan studies[8] reported an OR = 4.16 (95% CI 2.26–7.67) among the highest red meat consumers, after adjusting by calories. The increase of risk was even stronger for fried (OR = 5.31, 95% CI 2.77–10.2) than for broiled meat (OR = 2.21, 95% CI 1.18–4.14), however, there was no effect found for boiled meat, characteristic of stew (OR = 1.02, 95% CI 0.47–2.20). A possible effect of cooking at high temperatures was posed, a hypothesis sustained in our next paper by estimation of production of heterocyclic amines (HCAs) in the cooking process.[9] These substances (imidazoquinolin [IQ], fenylimidazopiridin [PHiP] and methylimidazo-quinoxalin [MeIQx]) displayed significant 2- to 3-fold risk increases for the high consumers. The risk associations were: for IQ an OR = 3.34 (95% CI 1.85–6.02), for PHiP an OR = 2.59 (95% CI 1.42–4.70) and for MeIQx an OR = 2.13 (95% CI 1.27–3.55). Among postmenopausal women, the increases of risk were even stronger for IQ (OR = 3.80, 95% CI 1.90–7.60) and for PHiP (OR = 3.31, 95% CI 1.60–6.87).

If meat consumption plays any role in the etiology of BC, it is possible that the risk could be related to meat, not as a fat and protein source, but preferably as a source of mutagens and/or carcinogens, specifically HCAs, N-Nitroso compounds and polycyclic aromatic hydrocarbons. Some HCAs are powerful mammary carcinogens in rodents,[70] have affinity for the mammary gland and could be risk factors for BC in humans. Currently, we accept that meat-rich diets, in particular red meat cooked with direct heating, increase the risk of BC.

Poultry

The literature has been relatively inconclusive about the relationship between poultry consumption and BC risk. In general, no association was found between the intake of poultry and the disease.[71] We studied the intake of chicken[16] in Uruguay, as a result of which important differences were described. Firstly, chicken with skin prevailed among BC cases, whereas controls without cancer preferred mostly skinless chicken ($p = 0.0008$). The high intake of chicken with skin displayed an increase of risk (OR = 1.54, 95% CI 0.86–2.77, p for trend 0.02), while the high intake of skinless chicken was associated to a reduction of risk (OR = 0.42, 95% CI 0.23–0.79, p for trend 0.04). In contrast, total chicken was associated to a non-significant reduction of risk of BC (OR = 0.78, 95% CI 0.42–1.47, p for trend 0.056). The preparation and consumption forms constitute a probable explanation for the absence of association reported in studies, including the prior Uruguayan studies. This could be based on the presence of fats in the chicken skin, as well as the production of HCAs in the skin surface, due to the cooking method. It is not unlikely that despite the preparation form, potential protection might derive from skinless poultry meat as well a potential damage could derive from this meat having its skin.

Feeding conditions for animals might represent an additional reason for the inconsistencies reported in the literature. Currently, poultry are usually exposed to special methods to enhance their growing process and development, which include supplements of corn seeds and other products while they are confined to reduced spaces. As consequence, their flesh can accumulate high contents of Ω-6 PUFAs instead of the natural Ω-3 PUFAs that would derive from eating a variety of their animal and vegetable sources if they could grow free in farms. In conclusion, it has still not been defined whether diets high in poultry have any association with BC. Preparation forms could be related to the disease.

Fish

Some epidemiologic studies suggest that high consumption of fatty fish is associated with a reduced risk for breast cancer[65,72] but usually results refer lack of association to BC.[73–75] Moreover, most experimental research supports a possible protective effect for the fish oil in the mammary tumorigenesis[76] The contribution of Ω-3 PUFAs, as will be described further, could be a possible explanation of the observed protective effects.

A study in Uruguay[16] revealed that the intake of not fried fish prevailed among controls ($p = 0.008$). While the latter was significantly protective (OR = 0.48, 95% CI 0.24–0.93), fried fish increased the risk of BC significantly (OR = 1.99, 95% CI 1.02–3.88)[16] Such difference in cooking methods might be also based on the imbalance of Ω-6/Ω-3 PUFAs they imply: fried fish usually belong to lean species (which are low Ω-3 contributors), and at the same time, the most common oils used to fry are sunflower and soy oil (which are high Ω-6 contributors). Hence, the result of this cooking method represents each time an intake of several Ω-6 grams which are not counterbalanced by dozens of Ω-3 milligrams.

Again, as it happens with poultry, similar considerations can be made about fish preparation and consumption forms: when they are queried together, several studies possibly do not show the difference that might actually exist, due to partial or total effect cancellation. It should be taken into account that cooking methods involving frying may determine the association of Ω-6 PUFAs to fish, with which the Ω-6/Ω-3 PUFAs ratio would lead to values that are potentially deleterious. Also, most studies on fish consumption and BC are limited by their lack of distinction between fatty (blue) and lean (white) fish. In short, although the evidence is considered still insufficient, fish-rich diets could reduce the risk of BC.

Dairy

Several studies analyzed the relationship between dairy products and the risk of BC. Evidence from more than 40 case-control studies and 12 cohort studies does not support an association between dairy product consumption and the risk of BC.[77]

A Uruguayan study[15] reported several associations between dairy foods and the risk of BC, most of them with an increase in risk: whole milk (OR = 2.84, 95% CI 1.38–5.84), chocolate milk (OR = 2.85, 95% CI 1.06–7.69), total milk (OR = 1.99, 95% CI 1.04–3.83), dambo cheese (OR = 1.66, 95% CI 0.86–3.19), gruyere cheese (OR = 1.93, 95% CI 1.05–3.55) and ice cream (OR = 1.98, 95% CI 1.07–3.66), mainly displaying a dose-response pattern. Besides, an inverse and significant association was found with skimmed yoghurt (OR = 0.29, 95% CI 0.15–0.58), total yoghurt (OR = 0.41, 95% CI 0.22–0.79) and ricotta cheese (OR = 0.45, 95% CI 0.24–0.83), also with a dose-response pattern. Although the fat intake pattern suggested by the dairy consumption might keep an obvious relationship, butter—the food item with the highest fat content—displayed an unexpected lack of association, suggesting that other components than fats could be also responsible for the risk association. Both intakes at age 18 showed rather similar results than in adulthood: while milk consumption was positively associated (OR = 2.66, 95% CI 1.39–5.08), butter consumption displayed a non-significant negative association (OR = 0.49, 95% CI 0.23–1.07).

Since other items (milk + yoghurt, total cheese, dairy) showed no association, results suggested that perhaps when epidemiologic

studies included items labeled as “milk”, “cheese” and “yoghurt” possible hidden differences coming from their varieties could have led results to the null. To summarize, the evidence on dairy consumption and BC is inconsistent, but according to our results skimmed and fermented products could reduce the risk of the disease.

Nutrients and bioactive substances

Fats

High-total fat diets possibly increase the risk of BC. Inconsistencies are shown by opposite results in different kinds of epidemiologic studies, but there are also directly or indirectly plausible biological mechanisms which have been proposed. Perhaps dietary fat intake may have more influence on BC risk when it occurs within an estrogen-rich environment. The relative distribution of various fatty acids seems to be more important as a risk factor for BC development than a high fat intake.[31] In particular, monounsaturated fat and the Ω-6/Ω-3 PUFAs ratio demonstrate more potential to influence BC risk.[32] Nevertheless, total fat has also been found to be associated to the risk of the disease.[78,79] Our study on fat intake[10] showed a non-significant increase in risk for the highest consumers of total fat (OR = 1.53, 95% CI 0.89–2.62), with a significant trend ($p = 0.01$).

Saturated fats

Since there are evidences of a positive association,[80] lack of association[81] and a protective effect of stearate[82,83] the evidence is not conclusive.[30] The Uruguayan study[10] showed no association between saturated fat intake and the risk of BC (OR = 0.89, 95% CI 0.34–2.07, p for trend 0.56).

Monounsaturated fats

In countries where populations have a typical Mediterranean diet (such as Spain, Greece and Italy, where virgin olive oil is the principal source of fat) cancer incidence rates are lower than in northern European countries.[84] The belief that the protective effect of olive oil is based on the high content (72% in average) of a monounsaturated fatty acid (MUFA), oleic acid, has its weakness. Such fat (also called Ω-9 fat) can be found in non negligible amounts (22–53%) in the fat of beef, chicken (even in the skin) and also in other vegetable oils as corn, peanut, soy and sunflower ones, within the range of 23–50%. The problem is posed by the fact that several fats and oils rich in oleic acid are highly associated with increased risks of breast and colon cancer in humans. In fact, our study on fat intake[10] showed a non-significant increase of risk for the highest quartile of MUFA (OR = 1.50, 95% CI 0.69–3.23, p for trend 0.55), which could be expected having in Uruguay staple foods as meat and sunflower oil. Besides, recent studies remark that oleic acid can suppress the overexpression of HER2 (erbB-2), a well-characterized oncogene playing a key role in the etiology, invasive progression and metastasis in several human cancers.[85,86]

Polyunsaturated fats

The Ω-6 (linoleic) and Ω-3 (α-linolenic) PUFAs are essential fatty acids. Arachidonic acid is the final Ω-6 PUFA, as well as docosahexaenoic (DHA) and eicosapentaenoic acid (EPA) are the final Ω-3 ones. While arachidonic is easily synthesized, the human body has inefficient mechanisms to convert α-linolenic acid into DHA and EPA. Original sources of DHA and EPA are fishes like salmon, herring, trout, tuna, sardines, mackerel and codfish. The benefic role of sufficient Ω-3 PUFAs and the deleterious one of excessive Ω-6 PUFAs is due to their derived eicosanoids (prostaglandins, tromboxanes, leukotrienes), which are the final effectors of the PUFAs' actions.[87] Some populations which have a high intake of foods that are Ω-3 sources are less afflicted with BC.[84] Recent research found that the combination of a high level of Ω-3 (in sea animals), low level of Ω-6 (in vegetable fats) and a high intake of monounsaturated fats (in olive oil)—which are components of Mediterranean diet—were a potent “anti-HER 2 cocktail”.[88]

Our study on essential fatty acids,[10] performed in women of the public hospital system reported an increase of risk associated to high intake of α-linolenic acid (OR = 2.76, 95% CI 1.08–7.03) and also a risk reduction for high intake of linoleic acid (OR = 0.24, 95% CI 0.12–0.45). Another study in women of the prepaid healthcare system in Uruguay[17] has also found a stronger negative association of high consumption of Ω-3 PUFAs (EPA + DHA) among younger women (less than 54 yrs old) than for the older ones (OR = 0.20, 95% CI 0.04–0.96 vs. OR = 0.67, 95% CI 0.26–1.76 respectively). The odds ratio for the highest tertile of intake of Ω-6 PUFAs was also higher among the younger subset than the older one (OR = 7.20, 95% CI 1.45–35.7 vs. OR = 4.05, 95% CI 1.65–9.94 respectively). As a consequence, the highest tertiles of Ω-6/Ω-3 ratio displayed a positive association among pre-menopausal women (OR = 5.51, 95% CI 1.77–17.2), but not among postmenopausal ones (OR = 1.09, 95% CI 0.55–2.13). The evidence suggests a risk association of Ω-6 PUFAs and a protective effect of Ω-3 PUFAs with the risk of BC.

Cholesterol

The analysis of several cohort studies has not shown an association with cholesterol intake. Although most studies which examined cholesterol intake[29,30,89] have not communicated any significant association either, in the Uruguayan study[10] the highest cholesterol intake showed significant risk increase (OR = 4.31, 95% CI 2.11–8.81), stronger than for other fat components like α-linolenic acid (OR = 2.76, 95% CI 1.08–7.03), monounsaturated fat (OR = 1.50, 95% CI 0.69–3.23) or saturated fat (OR = 0.84, 95% CI 0.34–2.07). We accept that cholesterol-rich diets could be associated with the risk of BC, but any conclusions seem premature.

Carotenoids

The relationship between β-carotene or carotenoids and the risk of BC has been assessed in different studies.[90–95] Lycopene intake was one of the strongest protective habits in Uruguayan women's diet (OR = 0.30, 95% CI 0.19–0.47). Also β-cryptoxanthin (OR = 0.52, 95% CI 0.34–0.80) and α-carotene (OR = 0.52, 95% CI 0.34–0.80) were significantly associated. Lutein/Zeaxanthin (OR = 0.66, 95% CI 0.43–1.01) and β-carotene (OR = 0.72, 95% CI 0.47–1.10) also showed negative but non-significant associations.[12] Since lycopene could partially explain the effect of total vegetables, and taking into account that this carotenoid prevails in tomatoes, we analyzed the risk associated with tomato and rich-tomato foods (i.e. pasta, pizza). The intake of fresh tomatoes was associated with a moderate and non-significant risk reduction (OR = 0.62, IC 0.36–1.06), whereas foods dressed with tomato sauce displayed a strong and significant protective effect (OR = 0.30, IC 0.17–0.52). Results were consistent with Howe et al's, who stated that lycopene in tomato products cooked with oil were better absorbed than from raw tomatoes.[96] Considering the evidence, we accept that high dietary levels of carotenoids probably reduce the risk of BC.

Phytoestrogens

Phytoestrogens are weak estrogens whose source are mainly vegetables and can be found in soybeans and unrefined cereals, as well as in some seeds (flaxseed, especially). The main phytoestrogens are isoflavones (daidzein, genistein), coumestans and lignans (enterolactone and enterodiol). Cereals and dietary fiber constitute an important source of lignans, and are high in legumes. Foods which are sources of phytoestrogens also were negatively associated to BC risk[14]: cereals (OR = 0.27, 95% CI 0.12–0.59),

vegetables (OR = 0.47, 95% CI 0.30–0.73), legumes (OR = 0.53, 95% CI 0.35–0.81) and fiber (OR = 0.29, 95% CI 0.19–0.46). Tubers did not show a protective effect (OR = 0.91, 95% CI 0.56–1.51). In Uruguay, research focused mainly in exploring lignans,[14] the most common ones in the Uruguayan diet. These substances displayed strong risk reductions for the highest intake levels: enterodiol (OR = 0.43, 95% CI 0.27–0.66), enterolactone (OR = 0.55, 95% CI 0.36–0.85), total lignans (OR = 0.43, 95% CI 0.27–0.67) and also isoflavones (OR = 0.62, 95% CI 0.40–0.95). Of them, significance was found only among postmenopausal women.

Vitamin D

Lack of sun exposure, which would mean a deficiency of vitamin D (VD), has been suggested as a possible risk factor for BC. Some studies found a strong inverse correlation between BC and availability of sun radiation necessary for VD synthesis in the skin.[97,98] These authors suggested that inadequate amounts of VD -associated to a low average intake- could be a significant risk factor for BC. Besides, a recent analysis recognized the potential role of VD in the prevention of BC.[99] However, new studies are needed for example, to find an optimal VD status and to define its appropriate biomarkers in relation to protection against BC.[100] The relationship with body fat content has been also studied: obesity increases the risk of VD deficiency.[101] Once the vitamin is synthesized in the skin or orally administered it is stored in the body fat depots, making it less available for subjects with high depots. Studies performed in Uruguay in healthy pre-menopausal women[102] and in post-menopausal women,[103] revealed insufficient levels of serum VD with more marked deficit in the cold seasons. This fact led the authors to consider the quoted low level of the hormone as a potential risk factor or BC for Uruguayan women, which was cited in a recent review on VD and BC.[19]

The literature links VD tightly with some of the major features of the insulin resistance syndrome. This metabolic frame provides a biological basis to think that the frequent situations of insulin resistance, BC and low VD levels are related to each other. Considering that human breast cells have VD receptors, and that many tumors express higher receptor levels than healthy tissues, there is a biologically plausible basis for the hypothesis that VD has a protective effect against BC. In summary, there is currently important epidemiologic and experimental evidence supporting a preventive role for VD.[19]

Anthropometric basis

Anthropometry is considered to be associated with the risk of BC. In the last years the association between body mass index (BMI) and BC was systematically examined by experts.[29,30] The evidence is showing a strong contrast: heavier women are at an increased risk of postmenopausal BC in most studies, whereas a high BMI represents a reduced risk among pre-menopausal women.[104–106] Studies in pre-menopausal women revealed a lack of association for some anthropometric measures (body size, BMI, fat distribution) in some populations, such as Chinese,[107,108] Japanese,[109] or African-American women.[110] Different results were reported in Caucasian women from Western nations. Recently, waist-to-hip ratio was also associated with an increase of risk in pre-menopausal Nigerian[111] and Asian-American women.[112]

Body composition was associated with 2-αOH- and 16-αOH-estrone levels: while thicker skinfolds were associated with higher 16-αOH levels,[113] an increase in lean body mass was associated with an improvement in 2/16-αOH estrogens ratio.[114] It has been suggested that women at higher risk for developing BC due to low 2/16-αOH estrogens may reduce their risk by participating in lifestyle interventions such as exercise/calorie restriction.[115]

Body composition

A recent Uruguayan study[22] reported a negative association of muscle fraction with the risk of BC (OR = 0.23, 95% CI 0.15–0.34), while the fat fraction and the fat-to-muscle ratio (FMR) were positively associated with this risk (OR = 3.90, 95% CI 2.62–5.80 and OR = 4.45, 95% CI 2.99–6.62 respectively), always displaying significant linear trends ($p < 0.0001$). The positive association of FMR was found stronger among obese women (OR = 6.09, 95% CI 2.66–13.9) than in overweight ones (OR = 4.86, 95% CI 2.20–10.7) or in normal weight ones (OR = 3.10, 95% CI 1.70–5.66). Increase of risk found for FMR suggested us that both, fraction and amount of the original components of weight, might play a role as possible risk factors. Our findings related to the muscle fraction lead to think about a protective role for the muscle mass. In response to contraction the muscle produces some cytokines called "myokines"[116,117] which are able to modulate the metabolic and immunological response to exercise in several tissues. One of them, Interleukin (IL)-6 works in a hormone-like fashion inducing lipolysis and fat oxidation, also enhancing the synthesis of anti-inflammatory cytokines and suppressing TNF-alpha production.[118] Besides, IL-15 participates in the reciprocal metabolic regulation between adipose tissue and skeletal muscle, by stimulating muscle fibers to accumulate increased amounts of proteins,[119] inducing T-cell proliferation,[120] enhancing NK cell cytotoxicity[121] and protecting these immune cells and neutrophils from apoptosis.[122,123] IL-15 could play an important role in the control of fat deposition in adipose tissue according to animal studies which showed differences between normal and obese animals.[124]

Skeletal muscle is able to produce and release glutamine in significant amounts (70–90% of the whole body pool).[125] Leukocytes use glutamine at high rates[126] and the differentiation of B-lymphocytes into antibody synthesizing and secreting cells is glutamine-dependent.[127] On this basis we have hypothesized that women with reduced and low active skeletal muscle mass (sedentary ones) might have higher risks of BC, since they could have been chronically exposed to a double inadequacy: a reduced glutamine support for their immune cells as well as a lesser control on lipolysis and fat deposition.[22]

Somatotype

A greater upper or central body fat distribution has been reported in the literature mainly as associated with multiple hormonal and metabolic changes including insulin resistance, hyperinsulinemia, reduction of sex hormone-binding globulin levels, increase in androgen levels, and the conversion of androgen to estrogen in adipose tissue.[128–130] Therefore, women having this pattern associated with increased risk for diabetes mellitus, hypertension and cardiovascular disease may have theoretically higher risks of BC than women whose fat is mainly distributed over hips, buttocks, and lower extremities. Since BC is a multifactorial disease, a Western lifestyle may act on the incidence of BC through an influence on body fat distribution and resulting changes in sex steroid availability.[131]

Besides, we have found that certain body measurements were associated with BC risk among the Uruguayan population, regardless of the menopausal status and BMI level, using the somatotype method.[21] To our knowledge, this was the first report on anthropometry and BC using this method. Cancer cases showed a higher endomorphy (adipose concentration mainly in hips, buttocks and thighs) than healthy controls. Endomorphy displayed positive associations with BC risk for the whole sample (OR = 2.82, 95% CI 1.70–4.70), stronger among pre-menopausal women (OR = 4.98, 95% CI 2.25–11.0) and among women with normal body weight (OR = 5.12, 95% CI 1.38–19.0), with a dose-response pattern in all

analyses. However, heterogeneity tests have not demonstrated differences between subsets in any of both analyses. Taking into account, on one hand, that mean weight values for cases and controls were similar and, on the other hand, that the selected skinfolds were notably thicker among cases, there is evidence for a different distribution of their weight, taking into account the adipose component.

We found that a high endomorphy (quite similar to the gynoid-type obesity) was positively associated with the risk of BC. Regarding this, a higher aromatase activity occurring in these body regions[132] could be a plausible explanation for the reported results. We also found similar waist-to-hip ratios in cases and controls, not suggesting differences regarding their central-type obesity. These somehow unexpected results enable us to think that ethnicity factors should be taken into account, in view of the different ancestries that Uruguayan women have when compared with North Americans, Scandinavians or others from first world countries.

Facing the future

Favorable evidence has been reported in the last years, regarding the potential utility of diet, weight management and physical activity in BC survival.[133–140] The rationale for using Ω-3 PUFAs in cancer prevention and treatment was discussed in a recent review.[141] According to the existing evidence, if there were positive results in the short lapses in which survival was analyzed—disease-free and global one—age should not be an obstacle to perform an attempt towards primary prevention through a nutritional strategy.

There would be basically two main dietary orientations: a "far Eastern" style (based on an increase of soy-derived products as beans, flour, tofu) or a "Mediterranean" style (based on fish and sea foods, olive oil, tomatoes). This latter, which is not strictly a low-fat style, is also related to the main ancestors of the Uruguayan population (Spain and Italy). When compared to the former style, diets having a long co-evolution of antigen tolerance would be advantageous.[31] Substitution of common oils by extra virgin olive oil in the preparation of foods might constitute a strong advance towards protection against BC, considering the evidence in the last fifteen years.

From our viewpoint, the following changes could be of utmost importance for the population: increasing the intake of Ω-3 fatty acids, tomatoes and citrus fruits; dramatically reducing the Ω-6 fatty acids by replacing common vegetable oils with extra virgin olive oil; reducing the red meat – grilled, barbecued or fried – intake; having an intake of white meat not prepared with direct heat; having an intake of skimmed dairy products; including a supplementation of vitamin D; avoiding alcohol consumption; having a low intake of high-glycemic index foods; and achieving as well as maintaining an adequate adipose level through some physical exercise.

We should remark that, to our knowledge, there are no published studies indicating that a prudent diet is risky or pejorative for health: some studies report negative associations (reductions in the risk of developing the disease or improvements in the disease-free survival as well for the global survival), and some other studies find no associations. No secondary effects derived from prudent diets have been described. This is a relevant difference with testing a pharmaceutical drug or other sort of therapy, for which we must evaluate pros and cons, in order to assure a favorable cost/benefit ratio for patients. Considering a vegetable- and fruit-rich eating style, the worst possible scenario would be the absence of a protective effect. But no health damage is expected to be suffered as a consequence of it. Furthermore, some additional benefits regarding cardiovascular and metabolic risks are expected to occur. Thus, if the proposed change has no risks, there would be no solid arguments for not encouraging women (with or without BC) to try a nutritional change, as an attempt to reduce the risk of developing BC or even also as an attempt to increase survival rate.

We should emphasize that the proposed nutritional changes involve not only the woman herself (who is not always a patient) but also the family nucleus she lives with. That will allow any kind of dietary modifications to be more acceptable and feasible to execute. One of the major issues is daughters: they could reduce the time of exposure to an inadequate dietary style, if there actually was any at present. If the woman has been afflicted with a BC, the benefit for the daughters is high, because history of BC in the mother implies a higher risk of the disease for those daughters. In the future it will not be the same if a woman with a high family risk follows an adequate nutritional style than if a woman continues displaying excessive and defective nutritional patterns. This could be called *transgenerational* prevention, and it is an obligation for authorities to think of the next generation's health, profiting from the existing knowledge.

Epigenetic changes of DNA and histones, as example of inheritable alterations in gene expression that do not involve changes in DNA sequences, are known to be involved in cancer. Two important epigenetic changes that contribute to disease are abnormal methylation patterns of DNA and modifications of histones in chromatin. Epimutations, such as the hypermethylation and epigenetic silencing of tumor suppressor genes, have revealed new areas for interventions, considering therapies or strategies for disease control. Dietary exposure during pregnancy and puberty may play an important role in determining later risk by inducing epigenetic changes that modify vulnerability to BC.[142] For example, prepubertal exposure to estradiol or genistein leads to a long-lasting up-regulation of BRCA1 mRNA in the rat mammary gland,[143] suggesting an increase in DNA repair capacity. Therefore, the exposure of a child or adolescent daughter to a protective dietary style will generate a stronger risk reduction than the one achievable by adult women. All the years of difference between the ages of the mother and the daughter (namely 20 to 35 years) run favorably towards the latter. With this long-term period of healthier exposure, the next generation could achieve a risk level which would be lower than their prior one. Furthermore, this concept should be expanded: intrauterine life is now also important concerning BC risks. An experimental study on rats showed years ago that the generation delivered by mothers fed with high Ω-6 PUFAs rich diets had puberty onset at a younger age, more terminal end buds in their glands and a higher frequency of BC than those ones fed with a standard diet.[144] On the contrary, a diet supplemented with Ω-3 PUFAs reduced the cancer risk in the next generation, showing more mammary gland differentiation.[145] An extrapolation from the animal model to humans enabled us to think that the potentiality of risk increase or reduction to develop the disease from intrauterine life is feasible and it might be modulated beginning with a dietary style. Probably adult intake of some bioactive dietary components reduces cancer risk increased by early life dietary exposure, or inhibits tumour growth by reversing epigenetic changes in various molecular targets.[146]The rationale for dietary interventions mainly centered on energy expenditure, fat intake and plant intake was recently reviewed.[147]

The possibilities of a tailored protective dietary style for a close future might exist, led by nutrigenomics of BC. It would have three potential targets to impact: hormonal, metabolic and toxic. Recent epidemiologic studies have reported that certain genetic polymorphisms in several genes encoding biotransformation enzymes are or could be associated to an increased risk of developing BC.[40] However, the identification of those who will or will not benefit from dietary intervention strategies remains a major obstacle. Adequate knowledge about how the responses depend on an individual's genetic background (nutrigenetic effects), as well as

the cumulative effects of food components on genetic expression profiles through nutrigenomics, may assist in identifying responders and non-responders.

Concluding remarks

Based on all the aforementioned concepts, accepting that a preventive strategy for BC is covered only by having periodical medical consultations and mammograms seems inadequate. Achieving an impact on the nutritional field means doing something else for breast health than early detection. A primary prevention strategy added to secondary prevention will allow for even better results, not only in reducing mortality but also contributing to a reduction in incidence. There are several challenges (i.e. behavioural) to be faced in order to achieve the success of such nutritional prevention. Our ultimate goal is to support an intervention strategy for breast health promotion that is culturally appropriate for a specific population. What we are proposing to do in primary prevention is mainly a quantitative and qualitative change in the bioavailability and exposure to the own estrogens, in other words, to manage fewer and better hormones.

Mass and sustained nutritional changes are needed to achieve any effect on the incidence of BC. Undoubtedly—at least, considering what depends on this factor—we cannot expect immediate changes about the current situation of the disease. Assuming the best possible scenario, if there were a mass change of habits directed towards a healthy style, we might be able to witness a reduction in incidence rates among some populations after the next 20 years. These processes take long time, thus, the perspective from the current knowledge suggests that it would be risky to suggest such a prognosis before the aforementioned time.

The existing literature has enabled us to express the potential convenience of some recommendations that are aligned with the general ones suggested internationally,[29,30] but that are also different from them, since the background of ours combines international with local evidences. Particular emphasis was placed on findings derived from local epidemiological studies. It would be convenient to recommend on this basis, if it is feasible to do so. It makes no sense to wait still ten years or more to suggest recommendations, when probably some significant international studies will show positive results, especially if such recommendations are of high additional benefit to vessels, metabolism, joints and as protection against developing other cancers. In the meantime, it is medically and ethically justified to recommend some nutritional changes to patients and to healthy women. This would at least constitute an attempt at low cost intervention without adverse side effects, contrary to those one can expect from drug treatments. While there is no clear evidence that any specific dietary component can effectively reduce BC risk,[148] the fact that several measures have convergence on the control of amount and quality of estrogens is something we can profit from.

Published studies show that a healthy dietary pattern and an adequate body composition can be either protective or not associated with the risk of BC. Nevertheless, since there are no studies – to our knowledge – showing that an apparently healthy lifestyle increases the risk of BC, any type of counterargument avoiding or discouraging this possible strategy from consideration for primary prevention of the disease sounds weak and unsupported.

Conflict of interest statement

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References

1. Ferlay J, Bray F, Pisani P, Parkin DM. *GLOBOCAN 2002: cancer incidence, mortality and prevalence worldwide IARC CancerBase No. 5*. Version 2.0. Lyon: IARC Press; 2004.
2. Parkin DM, Whelan SL, Ferlay J, Teppo L, Thomas DB, editors. *Cancer incidence in five continents*, vol. 8. Lyon: IARC Scientific Publications No. 155, IARC; 2002.
3. Food and Agricultural Organization, http://faostat.fao.org/site/610/DesktopDefault.aspx?PageID=610#ancor [Accessed 30.04.10].
4. United Nations Organization, Program of Human Development. Human development index rankings. Available at: http://hdr.undp.org/en/statistics/; 2009 [accessed 27.04.10].
5. U.S. Census Bureau. International data base, http://www.census.gov/ipc/www/idb/country.php [accessed 30.04.10].
6. Matos E, Brandani A. Review on meat consumption and cancer in South America. *Mutat Res* 2002;**506–507**:243–9.
7. Lafon L, Ronco AL. Analysis of geographic distribution of cancer in Montevideo. *Rev Med Uruguay* 2002;**1**:36–47 [in Spanish].
8. Ronco A, De Stéfani E, Mendilaharsu M, Deneo-Pellegrini H. Meat, fat and the risk of breast cancer: a case-control study from Uruguay. *Int J Cancer* 1996;**65**:328–31.
9. De Stéfani E, Ronco A, Mendilaharsu M, Guidobono M, Deneo-Pellegrini H. Meat intake, heterocyclic amines, and risk of breast cancer: a case-control study in Uruguay. *Cancer Epidemiol Biomarkers Prev* 1997;**6**:573–81.
10. De Stéfani E, Deneo-Pellegrini H, Mendilaharsu M, Ronco AL. Essential fatty acids and breast cancer: a case-control study in Uruguay. *Int J Cancer* 1998;**76**:491–4.
11. De Stéfani E, Correa P, Ronco A, Mendilaharsu M, Guidobono M, Deneo-Pellegrini H. Dietary fiber and risk of breast cancer. A case-control study in Uruguay. *Nutr Cancer* 1997;**28**:14–9.
12. Ronco AL, De Stéfani E, Boffetta P, Deneo-Pellegrini H, Mendilaharsu M, Leborgne Jr F. Vegetables, fruits, and related nutrients and risk of breast cancer: a case control study in Uruguay. *Nutr Cancer* 1999;**35**:111–9.
13. Ronco AL, De Stéfani E. Role of classic and dietary discriminant factors for classification of breast cancer high-risk populations: a study with neural networks. *Cancer Strategy* 1999;**1**:203–9.
14. Ronco AL, De Stéfani E. Phytoestrogens and risk of breast cancer: a case-control study. *Rev Med Uruguay*; 1999:94–102 [in Spanish].
15. Ronco AL, De Stéfani E, Dáttoli R. Dairy foods and risk of breast cancer: a case-control study in Montevideo, Uruguay. *Eur J Cancer Prev* 2002;**11**:457–63.
16. Ronco AL, De Stéfani E, Fabra A. White meat intake and the risk of breast cancer: a case-control study in Montevideo, Uruguay. *Nutr Res* 2003;**23**:151–62.
17. Ronco A, De Stéfani E, Deneo-Pellegrini H, Fabra A. Polyunsaturated fats consumption and risk of breast cancer: a case-control study. *Rev Bras Nutr Clin* 2005;**20**:S1–SS8. p. 12 [in Spanish].
18. Ronco A, De Stéfani E, Boffetta P, Deneo-Pellegrini H, Acosta G, Mendilaharsu M. Food patterns and risk of breast cancer: a factor analysis study in Uruguay. *Int J Cancer* 2006;**19**:1672–8.
19. Mendoza B, Ronco A. Vitamin D and breast cancer: a short review. *Biomedicina* 2007;**2**:139–48.
20. Ronco AL, De Stéfani E, Deneo-Pellegrini H. Fruit intake and risk of breast cancer: a case-control study. In: Fortugno Louis P, editor. *Frontiers in breast cancer research*. New York: Nova Science Publishers; 2008. p. 175–86.
21. Ronco AL, Mendoza B, Varas X, Jaumandreu S, De Stéfani E, Febles G, et al. Somatotype and risk of breast cancer: a case-control study in Uruguay. *Braz J Epidemiol* 2008;**11**:215–27.
22. Ronco AL, Boeing H, De Stéfani E, Schulz M, Schulze M, Pischon T. A case-control study on fat to muscle ratio and risk of breast cancer. *Nutr Cancer* 2009;**61**:466–74.
23. Torres-Sánchez L, Galván-Portillo M, Lewis S, Gómez-Dantés H, López-Carrillo L. Diet and breast cancer in Latin-America. *Salud Pub Mex* 2009;**51**:S181–S190 [in Spanish].
24. MacMahon B, Feinleib M. Breast cancer in relation to nursing and menopausal history. *J Natl Cancer Inst* 1960;**24**:733–53.
25. Tannenbaum A. Genesis and growth of tumors. III. Effects of a high-fat diet. *Cancer Res* 1942;**2**:468–75.
26. Hemminki K. Genetic and environmental factors in carcinogenesis. In: Vainio HU, Hietanen EK, editors. *Mechanisms in carcinogenesis and cancer prevention*. New York: Springer; 2003. p. 13–21.
27. De Stéfani E, Parkin DM, Khlat M, Vassallo A, Abella M. Cancer in migrants to Uruguay. *Int J Cancer* 1990;**46**:233–7.
28. Ronco A, Leibovici S, Vassallo JA. Cancer mortality in migrants to Uruguay. *Arch Med Int Urug* 1994;**16**:3107–12 [in Spanish].
29. World Cancer Research Fund. *Food, nutrition and the prevention of cancer: a global perspective*. Washington DC: American Institute for Cancer Research; 1997. p. 252–287.
30. World Cancer Research Fund/American Institute for Cancer Research. *Food, nutrition, physical activity, and the prevention of cancer: a global perspective*. Washington DC: American Institute for Cancer Research; 2007.
31. Hanf V, Gonder U. Nutrition and primary prevention of breast cancer: foods, nutrients and breast cancer risk. *Eur J Obstet Gynecol Reprod Biol* 2005;**123**:139–49.
32. Duncan AM. The role of nutrition in the prevention of breast cancer. *AACN Clin Issues* 2004;**15**:119–35.

33. Sepkovic DW, Bradlow HL. Estrogen hydroxylation – the good and the bad. *Ann N Y Acad Sci* 2009;**1155**:57–67.
34. Fishman J, Osborne MP, Telang NT. The role of estrogen in mammary carcinogenesis. In: Bradlow HL, Osborne MP, Veronesi U, editors. *Cancer prevention*. *Ann NY Acad Sci*; 1995:91–100.
35. Fishman J, Boyar RM, Hellman L. Influence of body weight on estradiol metabolism in young women. *J Clin Endocrinol Metab* 1975;**41**:989–91.
36. Bradlow HL, Hershcopf R, Fishman J. Oestradiol 16 alpha-hydroxylase: a risk marker for breast cancer. *Cancer Surv* 1986;**5**:573–83.
37. Muti P, Bradlow HL, Micheli A, Krogh V, Freudenheim JL, Schünemann H, et al. Estrogen metabolism and risk of breast cancer: a prospective study of the 2:16 alpha-hydroxyestrone ratio in premenopausal and postmenopausal women. *Epidemiology* 2000;**11**:635–40.
38. Bolton JL, Trush MA, Penning TM, Dryhurst G, Monks TJ. Role of quinones in toxicology. *Chem Res Toxicol* 2000;**13**:135–60.
39. Li KM, Todorovic R, Devanesan P, Higginbotham S, Köfeler H, Ramanathan R, et al. Metabolism and DNA binding studies of 4-hydroxyestradiol and estradiol-3,4-quinone in vitro and in female ACI rat mammary gland in vivo. *Carcinogenesis* 2004;**25**:289–97.
40. Parl FF, Dawling S, Roodi N, Crooke PS. Estrogen metabolism and breast cancer. A risk model. *Ann N Y Acad Sci* 2009;**1155**:68–75.
41. Dawling S, Roodi N, Mernaugh RL, Wang X, Parl FF. Catechol-o-methyltransferase (COMT)-mediated metabolism of catechol estrogens: comparison of wild-type and variant COMT isoforms. *Cancer Res* 2001;**61**:6716–22.
42. Hachey DL, Dawling S, Roodi N, Parl FF. Sequential action of phase I and II enzymes cytochrome p450 1B1 and glutathione S-transferase P1 in mammary estrogen metabolism. *Cancer Res* 2003;**63**:8492–9.
43. Cauley JA, Zmuda JM, Danielson ME, Ljung BM , Bauer DC, Cummings SR, et al. Estrogen metabolites and the risk of breast cancer in older women. *Epidemiology* 2003;**14**:740–4.
44. Liehr JG, Ricci MJ, Jefcoate CR, Hannigan EV, Hokanson JA, Zhu BT. 4-Hydroxylation of estradiol by human uterine myometrium and myoma microsomes: implications for the mechanism of uterine tumorigenesis. *Proc Natl Acad Sci USA* 1995;**92**:9220–4.
45. Liehr JG, Ricci MJ. 4-Hydroxylation of estrogens as marker of human mammary tumors. *Proc Natl Acad Sci USA* 1996;**93**:3294–6.
46. Fowke JH, Qi D, Bradlow HL, Shu X, Gao Y, Cheng JR, et al. Urinary estrogen metabolites and breast cancer: differential pattern of risk found with pre- versus post-treatment collection. *Steroids* 2003;**68**:65–72.
47. Falk RT, Fears T, Xu X, Hoover R, Pike MC, Wu AH, et al. Urinary estrogen metabolites and their ratio among Asian American women. *Cancer Epidemiol Biomarkers Prev* 2005;**14**:221–6.
48. Cascorbi I, Brockmöller J, Roots I. A C4887A polymorphism in exon 7 of human CYP1A1: population frequency, mutation linkages, and impact on lung cancer susceptibility. *Cancer Res* 1996;**56**:4965–9.
49. Hanna IH, Dawling S, Roodi N, Guengerich FP, Parl FF. Cytochrome P450 1B1 (CYP1B1) pharmacogenetics: association of polymorphisms with functional differences in estrogen hydroxilation activity. *Cancer Res* 2000;**60**:3440–4.
50. Jellinck PH, Forkert PG, Riddick DS, Okey AB, Michnovicz JJ, Bradlow HL. Ah receptor binding properties of indole carbinols and induction of hepatic estradiol hydroxylation. *Biochem Pharmacol* 1993;**45**:1129–36.
51. Bradlow HL, Sepkovic DW, Telang NT, Osborne MP. Indole-3-carbinol. A novel approach to breast cancer prevention. In: Bradlow HL, Osborne MP, Veronesi U, editors. *Cancer prevention*. *Ann N Y Acad Sci* 1995;**768**: 180–200.
52. McTernan PG, Anderson LA, Anwar AJ, Eggo MC, Crocker J, Barnett AH, et al. Glucocorticoid regulation of p450 aromatase activity in human adipose tissue: gender and site differences. *J Clin Endocrinol Metab* 2002;**87**:1327–36.
53. Wong GY, Bradlow HL, Sepkovic D, Mehl S, Mailman J, Osborne MP. Dose-ranging study of indole-3-carbinol for breast cancer prevention. *J Cell Biochem Suppl* 1997;**28**–**29**:111–6.
54. Ronco AL, De Stéfani E, Deneo-Pellegrini H, Mendilaharsu MS In: Ediciones De la Plaza, editor. *Nutritional epidemiology of breast cancer*; 2008. Montevideo. [in Spanish].
55. Key TJ, Allen NE, Spencer EA, Travis RC. The effect of diet on risk of cancer. *Lancet* 2002;**360**:861–8.
56. Wattenberg LW. Inhibition of neoplasia by minor dietary constituents. *Cancer Res* 1983;**43**:2448s–2453s.
57. Wattenberg LW, Schäfer HJ, Waters Jr L, Davis DW. Inhibition of mammary tumor formation by broccoli and cabbage. *Proc Am Assoc Cancer Res* 1989;**30**:181.
58. Sieri S, Krogh V, Pala V, Muti P, Micheli A, Evangelista A, et al. Dietary patterns and risk of breast cancer in the ORDET cohort. *Cancer Epidemiol Biomarkers Prev* 2004;**13**:567–72.
59. Hermann S, Linseisen J, Chang-Claude J. Nutrition and breast cancer risk by age 50: a population-based case-control study in Germany. *Nutr Cancer* 2002;**44**:23–34.
60. Aune D, De Stéfani E, Ronco AL, Boffetta P, Deneo-Pellegrini H, Acosta G, et al. Fruits, vegetables and the risk of cancer: a multisite case-control study in Uruguay. *Asian Pac J Cancer Prev* 2009;**10**:419–28.
61. Rohan TE, Howe GR, Friedenreich CM, Jain M, Miller AB. Dietary fiber, vitamins A, C, and E, and risk of breast cancer: a cohort study. *Cancer Causes Control* 1993;**4**:29–37.
62. Levi F, La Vecchia C, Gulie C, Negri E. Dietary factors and breast cancer risk in Vaud, Switzerland. *Nutr Cancer* 1993;**19**:327–35.
63. Van't Veer P, Kolb CM, Verhoef P, Schouten E, Hermus R, et al. Dietary fiber, beta-carotene and breast cancer: results from a case-control study. *Int J Cancer* 1990;**45**:825–8.
64. Freudenheim JL, Marshall JR, Vena JE, Laughlin R, Brasure J, Swanson MK, et al. Premenopausal breast cancer risk and intake of vegetables, fruits, and related nutrients. *J Natl Cancer Inst* 1996;**88**:340–8.
65. Engeset D, Dyachenko A, Ciampi A, Lund E. Dietary patterns and risk of cancer of various sites in the Norwegian European prospective investigation into cancer and nutrition cohort: the Norwegian women and cancer study. *Eur J Cancer Prev* 2009;**18**:69–75.
66. Gandini S, Merzenich H, Robertson C, Boyle P. Meta-analysis of studies on breast cancer risk and diet: the role of fruit and vegetable consumption and the intake of associated micronutrients. *Eur J Cancer* 2000;**36**:636–46.
67. Shen J, Gammon MD, Terry MB, Bradshaw P, Teitelbaum SL, et al. Telomere length, oxidative damage, antioxidants and breast cancer risk. *Int J Cancer* 2009;**124**:1637–43.
68. Aune D, De Stéfani E, Ronco AL, Boffetta P, Deneo-Pellegrini H, Acosta G, et al. Legume intake and the risk of cancer: a multisite case-control study in Uruguay. *Cancer Causes Control* 2009;**20**:1605–15.
69. Toniolo P, Riboli E, Shore RE, Pasternack BS. Consumption of meat, animal products protein, and fat and risk of breast cancer – a prospective cohort study in New York. *Epidemiol* 1994;**5**:391–7.
70. Snyderwine EG. Some perspectives on the nutritional aspects of breast cancer research: food-derived heterocyclic amines as etiologic agents in human mammary cancer. *Cancer* 1994;**74**:1070–7.
71. Missmer SA, Smith-Warner SA, Spiegelman D, Yaun SS, Adami HO, Beeson WL, et al. Meat and dairy food consumption and breast cancer: a pooled analysis of cohort studies. *Int J Epidemiol* 2002;**31**:78–85.
72. Kim J, Lim SY, Shin A, Sung M, Ro J, Kang H, et al. Fatty fish and fish omega-3 fatty acid intakes decrease the breast cancer risk: a case-control study. *BMC Cancer* 2009;**9**:216.
73. Terry P, Rohan TE, Wolk A, Maehle-Schmidt M, Magnusson C. Fish consumption and breast cancer risk. *Nutr Cancer* 2002;**44**:1–6.
74. Lund E, Engeset D, Alsaker E, Skeie G, Hjartaker A, Lundebye AK , et al. Cancer risk and salmon intake. *Science* 2004;**305**:477–8.
75. Wakai K, Tamakoshi K, Date C, Fukui M, Suzuki S, Lin Y, et al. Dietary intakes of fat and fatty acids and risk of breast cancer: a prospective study in Japan. *Cancer Sci* 2005;**96**:590–9.
76. Rose DP, Rayburn J, Hatala MA, Connolly JM. Effects of dietary fish oil on fatty acids and eicosanoids in metastasizing human breast cancer cells. *Nutr Cancer* 1994;**22**:131–41.
77. Parodi PW. Dairy product consumption and the risk of breast cancer. *J Am Coll Nutr* 2005;**24**:556S–568S.
78. Thiébaut AC, Kipnis V, Chang SC, Subar A, Thompson FE, Rosenberg PS, et al. Dietary fat and postmenopausal invasive breast cancer in the National Institutes of Health – AARP diet and health study cohort. *J Natl Cancer Inst* 2007;**99**:451–62.
79. Schulz M, Hoffmann K, Weikert C, Nöthlings U, Schulze MB, Boeing H. Identification of a dietary pattern characterized by high-fat food choices associated with increased risk of breast cancer: the European prospective investigation into cancer and nutrition (EPIC)-potsdam study. *Br J Nutr* 2008;**100**:942–6.
80. Sieri S, Krogh V, Ferrari P, Pala V, Thiebaut A, et al. Dietary fat and breast cancer risk in the European prospective investigation into cancer and nutrition. *Am J Clin Nutr* 2008;**88**:1304–12.
81. Löf M, Sandin S, Lagiou P, Hilakivi-Clarke L, Trichopoulos D, Adami HO, et al. Dietary fat and breast cancer risk in the Swedish women's lifestyle and health cohort. *Br J Cancer* 2007;**97**:1570–6.
82. Chajès V, Hultén K, Van Kappel AL, Winkvist A, Kaaks R, Hallmans G, et al. Fatty-acid composition in serum phospholipids and risk of breast cancer: an incident case-control study in Sweden. *Int J Cancer* 1999;**83**:585–90.
83. Evans LM, Toline EC, Desmond R, Siegal GP, Hashim AI, Hardy RW. Dietary stearate reduces human breast cancer metastasis burden in athymic nude mice. *Clin Exp Metastasis* 2009;**26**:415–24.
84. Willett WC. Dietary fat and breast cancer. *Toxicol Sci* 1999;**52**(Suppl.):127–46.
85. Menendez JA, Lupu R. Mediterranean dietary traditions for the molecular treatment of human cancer: anti-oncogenic actions of the main olive oil's monounsaturated fatty acid oleic acid (18:1n-9). *Curr Pharm Biotechnol* 2006;**7**:495–502.
86. Menendez JA, Papadimitropoulou A, Vellon L, Lupu R. A genomic explanation connecting "Mediterranean diet", olive oil and cancer: oleic acid, the main monounsaturated fatty acid of olive oil, induces formation of inhibitory "PEA3 transcription factor-PEA3 DNA binding site" complexes at the Her-2/neu (erbB-2) oncogene promoter in breast, ovarian and stomach cancer cells. *Eur J Cancer* 2006;**42**:2425–32.
87. Karmali RA. Eicosanoids in neoplasia. *Prev Med* 1987;**16**:483–502.
88. Menéndez JA, Vázquez-Martín A, Ropero S, Colomer R, Lupu R. HER2 (erbB-2)-targeted effects of the omega-3 polyunsaturated. Fatty acid alpha-linolenic acid (ALA; 18:3n-3) in breast cancer cells: the "fat features" of the "Mediterranean diet" as an "anti-HER2 cocktail". *Clin Transl Oncol* 2006;**8**:812–20.
89. Jakovljevic J, Touillaud MS, Bondy ML, Singletary SE, Pillow PC, Chang S. Dietary intake of selected fatty acids, cholesterol and carotenoids and estrogen receptor status in premenopausal breast cancer patients. *Breast Cancer Res Treat* 2002;**75**:5–14.

90. Gaudet MM, Britton JA, Kabat GC, Steck-Scott S, Eng SM, Teitelbaum SL, et al. Fruits, vegetables, and micronutrients in relation to breast cancer modified by menopause and hormone receptor status. *Cancer Epidemiol Biomarkers Prev* 2004;**13**:1485–94.
91. Mignone LI, Giovannucci E, Newcomb PA, Titus-Ernstoff L, Trentham-Dietz A, Hampton J, et al. Dietary carotenoids and the risk of invasive breast cancer. *Int J Cancer* 2009;**124**:2929–37.
92. Huang JP, Zhang M, Holman CD, Xie X. Dietary carotenoids and risk of breast cancer in Chinese women. *Asia Pacific J Clin Nutr* 2007;**16**:437–42.
93. Garland M, Willett WC, Manson JE, Hunter DJ. Antioxidant micronutrients and breast cancer. *J Am Coll Nutr* 1993;**12**:400–11.
94. Wang C, Baumgartner RN, Yang D, Slattery M, Murtaugh M, Byers T, et al. No evidence of association between breast cancer risk and dietary carotenoids, retinols, vitamin C and tocopherols in Southwestern Hispanic and non-Hispanic White women. *Breast Cancer Res Treat* 2009;**114**:137–45.
95. Sesso HD, Buring JE, Zhang SM, Norkus EP, Gaziano JM. Dietary and plasma lycopene and the risk of breast cancer. *Cancer Epidemiol Biomarkers Prev* 2005;**14**:1074–81.
96. Howe GR, Hirohata T, Hislop TG, Iscovich J, Yuan JM, Katsouyanni K, et al. Dietary factors and risk of breast cancer: combined analysis of 12 case-control studies. *J Natl Cancer Inst* 1990;**82**:561–9.
97. Garland C, Garland F, Gorham E. Epidemiology of cancer risk and vitamin D. In: Holick M, editor. *Vitamin D: molecular biology, physiology, and applications*. Totowa, NJ: Humana Press; 1999. p. 375–409.
98. John EM, Schwartz GG, Dreon DM, Koo J. Vitamin D and breast cancer risk: the NHANES I epidemiologic follow-up study, 1971–1975 to 1992. National health and nutrition examination survey. *Cancer Epidemiol Biomarkers Prev* 1999;**8**:399–406.
99. Zhang SM. Role of vitamins in the risk, prevention, and treatment of breast cancer. *Curr Opin Obstet Gynecol* 2004;**16**:19–25.
100. Welsh J. Vitamin D and breast cancer: insights from animal models. *Am J Clin Nutr* 2004;**80**:1721S–1724S.
101. Arunabh S, Pollack S, Yeh J, Aloia JF. Body fat content and 25-hydroxyvitamin D levels in healthy women. *J Clin Endocrinol Metab* 2003;**88**:157–61.
102. Mendoza B, Ronco AL. Importance of vitamin D3 serum levels. *Tendencias en Medicina* 2001;**IX**:97–101 [in Spanish].
103. Mendoza B, Ronco AL, Mintegui G, Belzarena MC. Serum vitamin D status among postmenopausal Uruguayan women. International Osteoporosis Foundation World Congress; June 2–6, 2006, Toronto, Canada. Abstract p704su, p. S208.
104. Macinnis RJ, English DR, Gertig DM, Hopper JL, Giles GG. Body size and composition and risk of postmenopausal breast cancer. *Cancer Epidemiol Biomarkers Prev* 2004;**13**:2117–225.
105. Lahmann PH, Hoffmann K, Allen N, van Gils C, Khaw K, Tehard B, et al. Body size and breast cancer risk: findings from the European prospective investigation into cancer and nutrition (EPIC). *Int J Cancer* 2004;**111**:762–71.
106. Lahmann PH, Schulz M, Hoffmann K, Boeing H, Tjonneland A, Olsen A, et al. Long-term weight change and breast cancer risk: the European prospective investigation into cancer and nutrition (EPIC). *Br J Cancer* 2005;**93**:582–9.
107. Shu XO, Jin F, Dai Q, Shi JR, Potter JD, Brinton LA, et al. Association of body size and fat distribution with risk of breast cancer among Chinese women. *Int J Cancer* 2001;**94**:449–55.
108. Chow LW, Lui KL, Chan JC, Chan TC, Ho PK, Lee WY, et al. Association between body mass index and risk of formation of breast cancer in Chinese women. *Asian J Surg* 2005;**28**:179–84.
109. Hirose K, Tajima K, Hamajima N, Takezaki T, Inoue M, Kuroishi T, et al. Association of family history and other risk factors with breast cancer risk among Japanese premenopausal and postmenopausal women. *Cancer Causes Control* 2001;**12**:349–58.
110. Hall IJ, Newman B, Millikan RC, Moorman PG. Body size and breast cancer risk in black women and white women: the Carolina breast cancer study. *Am J Epidemiol* 2000;**151**:754–64.
111. Okobia MN, Bunker CH, Zmuda JM, Osime U, Ezeome ER, Anyanwu SN , et al. Anthropometry and breast cancer risk in Nigerian women. *Breast J* 2006;**12**:462–6.
112. Wu AH, Yu MC, Tseng CC, Pike MC. Body size, hormone therapy and risk of breast cancer in Asian-American women. *Int J Cancer* 2007;**120**:844–52.
113. Campbell KL, Westerlind KC, Harber VJ, Friedenreich CM, Courneya KS. Associations between aerobic fitness and estrogen metabolites in premenopausal women. *Med Sci Sports Exerc* 2005;**37**:585–92.
114. Campbell KL, Westerlind KC, Harber VJ, Bell GJ, Mackey JR, Courneya KS. Effects of aerobic exercise training on estrogen metabolism in premenopausal women: a randomized controlled trial. *Cancer Epidemiol Biomarkers Prev* 2007;**16**:731–9.
115. Westerlind KC, Williams NI. Effect of energy deficiency on estrogen metabolism in premenopausal women. *Med Sci Sports Exerc* 2007;**39**:1090–7.
116. Pedersen BK, Akerström TC, Nielsen AR, Fischer CP. Role of myokines in exerc and metab. *J Appl Physiol* 2007;**103**:1093–8.
117. Pedersen BK, Fischer CP. Physiological roles of muscle-derived interleukin-6 in response to exercise. *Curr Opin Clin Nutr Metab Care* 2007;**10**:265–71.
118. Pedersen BK. IL-6 signalling in exercise and disease. *Biochem Soc Trans* 2007;**35**:1295–7.
119. Quinn LS, Anderson BG, Drivdahl RH, Alvarez B, Argilés JM. Overexpression of interleukin-15 induces skeletal muscle hypertrophy in vitro: implications for treatment of muscle wasting disorders. *Exp Cell Res* 2002;**280**:55–63.
120. Burton JD, Bamford RN, Peters C, Grant AJ, Kurys G, Goldman CK, et al. A lymphokine, provisionally designated interleukin T and produced by a human adult T cell leukemia line, stimulates T cell proliferation and the induction of lymphokine-activated killer cells. *Proc Natl Acad Sci USA* 1994;**91**:4935–9.
121. Carson WE, Giri JG, Lindemann MJ, Linett ML, Ahdieh M, Paxton R, et al. Interleukin (IL) 15 is a novel cytokine that activates human natural killer cells via components of the IL-2 receptor. *J Exp Med* 1994;**180**:1395–403.
122. Akbar AN, Borthwick NJ, Wickremasinghe RJ, Panayiotidis P, Pilling D, Bofill M, et al. IL-2 receptor common gamma-chain signaling cytokines regulate activated T-cell apoptosis in response to growth factor withdrawal: Selective induction of anti-apoptotic (bcl-2, bcl-xL) but not pro-apoptotic (bax, bcl-xS) gene expression. *Eur J Immunol* 1996;**26**:294–9.
123. Girard D, Paquet ME, Paquin R, Beaulieu AD. Differential effects of interleukin-15 (IL-15) and IL-2 on human neutrophils: modulation of phagocytosis, cytoskeleton rearrangement, gene expression and apoptosis by IL-15. *Blood* 1996;**88**:3176–84.
124. Alvarez B, Carbó N, López-Soriano J, Drivdahl R, Busquets S, López-Soriano F, et al. Effects of interleukin-15 (IL-15) on adipose tissue mass in rodent obesity models: evidence for direct IL-15 action on adipose tissue. *Biochim Biophys Acta* 2002;**1570**:33–7.
125. Darmaun D, Matthews DE, Bier DM. Glutamine and glutamate kinetics in humans. *Am J Physiol* 1986;**251**:E117–E126.
126. Newsholme P. Why is L-glutamine metabolism important to cells of the immune system in health, postinjury, surgery or infection? *J Nutr* 2001;**131**:2515S–2522S.
127. Crawford J, Cohen HJ. The essential role of glutamine in lymphocyte differentiation in vitro. *J Cell Physiol* 1995;**124**:275–82.
128. Brunning PF, Bonfrer JMG, van Noord PAH, Hart AA, de Jong-Bakker M, Nooijen WJ. Insulin resistance and breast cancer risk. *Int J Cancer* 1992;**52**:511–6.
129. Lorincz AM, Sukumar S. Molecular links between obesity and breast cancer. *Endocr Relat Cancer* 2006;**13**:279–92.
130. Vona-Davis L, Howard-McNatt M, Rose DP. Adiposity, type 2 diabetes and the metabolic syndrome in breast cancer. *Obes Rev* 2007;**8**:395–408.
131. Bruning PF. Endogenous estrogens and breast cancer a possible relationship between body fat distribution and estrogen availability. *J Steroid Biochem* 1987;**27**:487–92.
132. Killinger DW, Perel E, Daniilescu D, Kharlip L, Lindsay WR. The relationship between aromatase activity and body fat distribution. *Steroids* 1987;**50**:61–72.
133. Rock CL, Demark-Wahnefried W. Nutrition and survival after the diagnosis of breast cancer: a review of the evidence. *J Clin Oncol* 2002;**20**:3302–16.
134. Berrino F, Villarini A, De Petris M, Raimondi M, Pasanisi P. Adjuvant diet to improve hormonal and metabolic factors affecting breast cancer prognosis. *Ann N Y Acad Sci* 2006;**1089**:110–8.
135. Kroenke CH, Chen WY, Rosner B, Holmes MD. Weight, weight gain, and survival after breast cancer diagnosis. *J Clin Oncol* 2005;**23**:1370–8.
136. Holmes MD, Chen WY, Feskanich D, Kroenke CH, Colditz GA. Physical activity and survival after breast cancer diagnosis. *JAMA* 2005;**293**:2479–86.
137. Fink BN, Gaudet MM, Britton J, Abrahamson PE, Teitelbaum S, Jacobson J, et al. Fruits, vegetables, and micronutrient intake in relation to breast cancer survival. *Breast Cancer Res Treat* 2006;**98**:199–208.
138. McEligot AJ, Largent J, Ziogas A, Peel D, Anton-Culver H. Dietary fat, fiber, vegetable, and micronutrients are associated with overall survival in postmenopausal women diagnosed with breast cancer. *Nutr Cancer* 2006;**55**:132–40.
139. Skeie G, Hjartaker A, Lund E. Diet among breast cancer survivors and healthy women. The Norwegian women and cancer study. *Eur J Clin Nutr* 2006;**60**:1046–54.
140. Kushi LH, Kwan ML, Lee MM, Ambrosone CB. Lifestyle factors and survival in women with breast cancer. *J Nutr* 2007;**137**:236S–242S.
141. Berquin IM, Edwards IJ, Chen YQ. Multi-targeted therapy of cancer by omega-3 fatty acids. *Cancer Lett* 2008;**269**:363–77.
142. De Assis S, Hilakivi-Clarke L. Timing of dietary estrogenic exposures and breast cancer risk. *Ann N Y Acad Sci* 2006;**1089**:14–35.
143. Cabanes A, Wang M, Olivo S, De Assis S, Gustafsson J, Khan G, et al. Prepubertal estradiol and genistein exposures up-regulate BRCA1 mRNA and reduce mammary tumorigenesis. *Carcinogenesis* 2004;**25**:741–8.
144. Hilakivi-Clarke L, Clarke R, Onojafe I, Raygada M, Cho E, Lippman M. A maternal diet high in n-6 polyunsaturated fats alters mammary gland development, puberty onset, and breast cancer risk among female rat offspring. *Proc Natl Acad Sci USA* 1997;**94**:9372–7.
145. Hilakivi-Clarke L, Cho E, Cabanes A, De Assis S, Olivo S, Helferich W, et al. Dietary modulation of pregnancy estrogen levels and breast cancer risk among female rat offspring. *Clin Cancer Res* 2002;**8**:3601–10.
146. Hilakivi-Clarke L. Nutritional modulation of terminal end buds: its relevance to breast cancer prevention. *Curr Cancer Drug Targets* 2007;**7**:465–74.
147. Forman MR. Changes in dietary fat and fiber and serum hormone concentrations: nutritional strategies for breast cancer prevention over the life course. *J Nutr* 2007;**137**:170S–174S.
148. Mahoney MC, Bevers T, Linos E, Willett W. Opportunities and strategies for breast cancer prevention through risk reduction. *CA Cancer J Clin* 2008;**58**:347–71.