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Diet, obesity and breast cancer: an update

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1. ABSTRACT

Numerous studies indagated the relationship between dietary pattern or specific nutrients and breast cancer (BC) risk and survival. Different ethnic o social groups show differences in breast cancer incidence that could be explained by different dietary patterns. Furthermore, many nutrients could reasonably increase the risk of cancer because of their content of carcinogens or their precursors as well as of promoting substances. However, the only convincing evidences linking life style to increased BC risk are related to obesity and moderate intake of alcohol and limited to postmenopause. Saturated fat, red meat, high temperature cooking have been indicated as possible risk factors, but adjusted analyses have not confirmed this association or have limited the relationship to specific subgroups. Even the protective effect of fiber, fruit, vegetables and phytoestrogens has been suggested but not definitively demonstrated. Thus, healthy dietary patterns, with abstention from alcohol and weight control, reduce the risk of cancer or at least improve the survival of affected women by reducing the incidence of comorbidities.

2. INTRODUCTION

The relationship between nutrition and oncology, from pathogenesis to response to therapies, is usually investigated by epidemiologists, nutritionists, biologists, oncologists, and genetists, whereas surgeons show a poor interest in such issue. Nevertheless, the treatment of patients with BC and their long-term follow-up are still principally surgeon-centric. Thus, it is usually the breast-surgeon who is called to answer queries as " Is it true that milk proteins make BC grow?" or "Is it true that if I don't loose weight I will develop BC younger than my mother?". More generally breast-surgeon are also asked about the influence of life style on the development and outcome of BC. Questions are as numerous as the patients we see, and it is not easy provide an answer also because robust evidence is available for very few issues, being the rest poorly investigated or still controversial. The purpose of this study is to review the most significant and recent studies concerning the role of the diet on breast oncogenesis, age of onset of cancer, response to therapies and the survival.

3. METHODS

A Medline search, limited to English literature of the last three years, has been conducted using as key words BC, breast neoplasms, diet, food, obesity and energy intake. Among studies retrieved we selected reviews, case control studies, cohort studies and nested case control studies of at least 200 participants. We also included the experimental studies aimed to explore specific mechanism of action. Important previous studies cited in references by reviews have been included as well (Table 1).

4. THE HISTORICAL AND EPIDEMIOLOGICAL BASIS

The first to affirm an association between cancer and "bad food" was Gabriele Falloppio in the 16th century. This Italian scientist, anatomist, surgeon and botanist, included among bad food beef, meat, bitter and salt foods The interest for dietary habits as possible risk factor for cancer found a new impulse in the mid seventies of last century when Phillips and coll. published their study on risk of cancer among Seventh-Day Adventists (SDAs) (1). SDAs have very moderate habits. In fact, the all abstain from smoking and drinking, 50% of them are lacto-ovo-vegetarians and most of them avoid coffee, tea and hot spices. In SDA population cancer rates were about 50-70 % less than the observed general population for cancers unrelated to alcohol and tobacco. Although the differences in the risk to develop malignancies in SDA population were really striking, the same Authors subsequently reported that, after data adjusting for demographic and socio-economic factors, the difference persisted only for colorectal cancer, and it became scarcely significant for BC and other neoplasms (2,3). Another important evidence of the fundamental role played by environmental factors in the genesis of BC derives from the observation on immigrated women. Japanese women have a low risk of BC and this protection lasts for about two generations after migration in the western countries. The third generation usually reaches the same risk as the women of the host country (4). These observations suggest to investigate dietary habits of women in low risk countries compared to high-risk western countries and the habits of women with cancer compared with healthy controls.

Other epidemiologic studies investigated the association between obesity and BC and various mechanisms have been suggested to explain this association, especially in terms of excessive caloric intake. Analysis of dietary effects has been approached in many different ways, from a single nutrient to a dietary pattern. The interaction between different foods can account for the poor statistical significance of most of the studies (5,6). Also the method of case recruiting (case-control studies, nested case control, retrospective cohort studies) and collecting data (from scheduled periodical questionnaires to self assessment questionnaires based on personal recall of participants) are quite different. All these variables and even the type of mathematical evaluation can hide the reason for the often contradictory results (7,8).

5. OBESITY

The relationship between obesity and BC has been known for a long time. Countries with a recent increase in the rate of obesity are also showing a concomitant and alarming increase in BC frequency (9). Regardless of dietary patterns, a high BMI has been associated with a lower risk of developing BC in premenopausal women and with a higher risk in postmenopausal women 88,10,11). A recent paper estimated an increase relative risk of approximately 1.4 for postmenopausal BC for each 10 kg /m^2 increase in BMI (12). However, the way by which obesity can influence the risk is still controversial. In postmenopausal women, the mechanism could be related to the activity of aromatases present in adipous tissue, as well as in gonads and in breast tumors, on adrenal steroid. Androstenedione is produced by adrenal glands and by gonads. When ovaric production ceases, the adrenal production continues and the hormone is converted within adipous tissue in estradiol and estrone. The more adipous tissue is present, the more estrogens are produced thus maintaining a high level even after menopause and exposing the breast to their carcinogenic potential (13). Various other hypotheses have been proposed. One of these postulates the dysregulation of energy balance with altered cytokine and growth factor levels (14). Also the role of Insulin and insulin-like growth factor has been suggested. In obese post-menopausal women the intraabdominal fat determines an increase in insulin- resistance, and thus the pancreatic production of insulin. High insulin levels reduce the production of IGF-binding proteins 1 and 2, leading to an increased activity of IGF, reduction of sex hormone binding globulin production and eventually increased testosterone and estradiol levels, whose role in cell proliferation and inhibition of apoptosis have been suggested by various studies (11). The role of adiponectine has also been proposed but not confirmed (15). This could explain, at least for postmenopausal women, why energy dense foods, such as animal fat,

Table 1. cohort and case control studies and most relevant conclusion

Study[ref]	Author	Year	Cohort	menopausal status or age	cancers	controls	RR	follow up	Issue
Seventh day Adventists vs white Californian non SDA [2]	Phillips	1980	22.940/112.725	PreM and PostM			NR	17y/13y	Healthy diet vs Western diet
Seventh day Adventists vs white Californian non SDA [2, 3]	Mills	1989	20.341	PreM and PostM	215		NR	6	Obesity associated to postmenopausal cancer. Dietetic pattern
Canadian National Breast Screening Study [43]	Howe	1991	56.837	PreM and PostM	519		1,35	5 y	Total fat intake RA
New York State Cohort [45]	Graham	1992	18.586	PostM			NR	7 y	calories, vitamins A, C, or E, dietary fiber, or fat
Nurses' Health Study [46]	Willett	1992	89.494	age 34-59	1.439		NR	8y	Fat and fiber
Montevideo, Uruguay, case control study hospital based [60]	De Stefani	1997		20-89	365	382	3,34		heterocyclic amines and high fat intake increase BC risk. Vegetables intake reduces risk of BC
Iowa Women's Health Study [55]	Zheng	1998	41.386	PostM	273	657	1,54		Well done meat vs medium-rare done (HA)
The Swedish Mammography Screening Cohort.[137]	Terry	2001	61.463	age 40-76	1.328		1,27	9,6y	Dietary pattern NR. Alcohol increases the risk of BC
European Prospective Investigation into Cancer and Nutriton (EPIC)-Dutch cohort [98]	Keinan-Boker	2004	15.555	50-69	280 BC (549 Other cancers)			4-8y	Isoflavones : NR
Case control study from Erie and Niagara Counties [84]	Ambroson e	2004			740	810	0,6		Cruciferous consume lower risk in premenopausal women; NR in postmenopausal
Case-control from Hospital of Mexico City [65]	Romieu	2004		25-75	475	1391	2,22		Carbohydrates, especially sucrose and fructose are associated with higher risk of BC
Nurses Health Study II [25]	Frazier	2004	47.355				0,58-0,61;1,47		protective effects of vegetable fat and vitamin E; adverse effect of high glycemic foods
European Prospective Investigation Into Cancer and Nutrition (EPIC) [78, 138]	Van Gils	2005	285 526	25-70	3.659		0,98-1,09	10	Fruit and vegetables NR
Food and Agriculture Organization and World Health Organization. [22]	Zhang	2005							Milk NR
French Women cohort[139]	Touillaud	2007	58.049	postM	1.469		0,72-0,83	7 y	high Lignan intake reduces risk of ER- PR+ BC
Hormones and Diet in the Etiology of Breast Tumors Study (ORDET Study)[66]	Sieri	2007	8.926		289		3,89; 5,79		Glycemic index (GI) and Glycemic load (GL). Very relevant for GL in premenopausal normal BMI
Long Island case control study [56]	Steck	2007			1.508	1556	1,47		High temperature cooked meats associated with BC
Nurses' Health Study II [108]	Cho	2007	90.663	preM (26-46)	1.032			12	Folate, vitamin B6, vitamin B12, methionine, choline, and betaine NR
Population-based case-control study in German [36]	Abbas	2007			278	666	0,5		Vitamin D associated with lower risk, Calcium NR
UK Women's Cohort Study (UKWCS)[76]	Cade	2007	35.792	preM-postM	607 (257 and 350)		0,48		Fiber (Whole cereal and fruit) protective against BC in premenopausal

Western Pomerania [74]	Kruk	2007		28-78	858	1085			Protective effects of recreational physical activity, total vegetables or fruits intake, and intake of vitamins
California Teachers Study [120]	Horn-Ross	2008	44.423	postM	1.544		1,36	7y	Alcohol (20g/1000Kcal) increases the risk of BC
Danish Diet, Cancer and Health Study, a nested case control study [62]	Olesen	2008		postM	374	374	2.7		10 fold acrylamide- hemoglobin level related to increaseof ER+ BC
E3N [Etude Epidémiologique auprès des femmes de la Mutuelle Générale de l'Education Nationale (MGEN)] [70]	Lajous	2008	62.739	PostM	1.812		1,78	9y	increased risk of ER- PR- with higher consume of rapidly absorbed carbohydrates
EPIC [38]	Sieri	2008	319.826		7.119		1,21	8,8y	Saturated fat intake increases risk for post- menopausal who did not use HRT
European Prospective Investigation into Cancer and Nutrition (EPIC) -Potsdam[6]	Shultz	2008		preM-postM	137		2		high Fat intake increases risk
Long Island Breast Cancer Study Project (LIBCSP), case - control[114, 115]	Xu	2008		20-98	1.508	1556	0,76		high Choline intake vs lowest (in 2009 highest choline intake related with lowest mortality
Malmo Diet and Cancer cohort [53]	Sonestedt	2008	11.699	>50	430		1,83		HA NR; higher risk with low HA and high O-6-PUFA intake
Multiethniccase-control study from San Francisco Bayarea [39]	Wang	2008			1.703	2045	1,35 and 1,58		High fat intake vs low fat intake and linoleic acid vs oleic acid for cooking
Southerne France, case control study [26]	Bessaoud	2008			437	922	0,63		Raw fiber (63-103 g/day), olive oil have protective effect; meat increases risk by 56% EACH 100 G
Swedish Mammography Cohort [102]	Suzuki	2008	51.823	postM	1.284		0,83	8,3 y	High Lignans intake associated with lower risk, independent from HR status
Uppsala Health Care Region cohort [104]	Hedelin	2008	45.448	30-49	1.014			13	Dietary fiber and Phyto estrogen NR, Intermediate coumestrol intake associated with lower rate ER-PR- BC and higher of HR+
Barbados National Cancer Study Group [17]	Nemesure	2009		preM and postM	222	454	2,16		Body size: tall stature in postM increases the risk
Black Women's Health Study [75]	Agurs-Collins	2009	50.778		1.094		0,64	12	prudent pattern (whole grains, vegetables, fruit, and fish) vs Western diet (refined grains, processed meat, and sweets); greater protective effects against preM and ER-cancer
EPIC [23]	Pala	2009	319.826		7.119		1,10-1,28	8,8	Meat, eggs, dairy products NR, High temperature cooking read meat should be further investigated
EPIC [86]	Spencer	2009	114.504		3.747		0,93	9,5	grapefruit: highest intake vs no intake. NR
French Canadian Women, nested case-control study [121]	Bissonauth	2009			280	280	1,34		> 2 bottle of beer/week vs no alcohol, 1,09 for 6 oz of spirit/week
Guangdong case-control [140]	Zhang	2009		25-70	438	438	0,24		vegetable and fruit:vitamin C, vitamin E, vitamin A, fiber, and carotene : highest vs lowest intake
Long Island case control [67]	Bradshaw	2009			1.434	1440	1,27;		sweet foods and beverages and sugar: highest intake vs lowest. RR 2 for desserts in preM
National	Park	2009	185.598	postM	5.461		0,87;		Fiber from grains, fruit,

Institutes of Health-AARP Diet and Health Study[141]							0,56		vegetables, and beans , highest vs lowest intake, overall and for HR-
Prostate Lung colorectal and Ovarian Cancer Screening Trial Cohort [19]	Sue	2009	29.170	preM	1.319		1,21; 1,37; 1,55	4,4	Energy intake: highest vs lowest. Risk increases with the time
Shanghai Women's Health Study [142]	Moore	2009			248	1040	2,63		Iron stored (ferritin) and dietary: highest levels vs lowest. Present even for fibrocystic changes
Shanghai Women's Health Study, nested case-control [68]	Wen	2009	74.942	40-70	616		2,01	7,3	Carbohydrates: highest vs lowest intake. Relevant in <50y
Southwestern Hispanic and non-Hispanic, cse-control [80]	Wang	2009							Dietary antioxidant (vitamins) NR
Swedish Mammography Cohort [52]	Larsson	2009	61.433		2.952		1,45	17y	Overall meat (>98g vs <46g): NR. Fried meat: highest vs lowest intake (for ER+ PR-)R
Women's Health Initiative Observational Study (WHI-OS), nested case control study [72]	Gunter	2009	93.676	postM	835	816	1,46		insulin, glucose, total IGF-I, free IGF-I, IGF-1-BP; insulin highest level vs lowest
Cancer Prevention Study II Nutrition Cohort [110]	Stevens	2010	70.656	postM	3.898		1,12;		Folate , vitamin B-6, vitamin B-12, methionine, and alcohol.highest vs lowest intake, Potitive for folates (NR) and negative for methionine
European Prospective Investigation into Cancer and Nutrition (EPIC) [106]	Nagel	2010			7.502		0,88-1,1	8,8y	anti-oxidant (beta-carotene, vitamin C and vitamin E) , highestvs lowest intake. Some effect in postmenopausal with high alcohol consume
European Prospective Investigation into Cancer and Nutrition-Norfolk (EPIC-Norfolk); nested case-control study [94]	Ward	2010		40-79	244	941	0,97		Phytoestrogen: highest vs lowest intake: NR for BC
Hereditary Breast cancer Clinical Study Group [122]	Dennis	2010		prevalent preM	1925 and 1925		0,82		Alcohol in BRCA1 and BRCA2 carriers (matched pairs):wine associated with reduction in risk for BRCA1 carriers RA
Malmo Diet and Cancer Study, nested case-control [33]	Almquist	2010		preM and PostM	764	764	0,84		Vit. D., PTH and Calcium- vit.D highest vs lowest level
Nurses' Health Study [143]	Linos	2010	39.268	34-53	455		1,35		Dietary fat consumed during adolesce has RA with BC
Ontario Cancer Registry.[35]	Anderson	2010		25-74	3.101	3471	0,76		Vit. D., and Calcium. vit D from supplements highest vs lowest intake , NR

Ref: reference, BC = Breast Cancer, PreM= Premenopausal, PostM =Postmenopausal, HR = Hormonal Receptor, DP = Dietary pattern, NR= non.relevant, RA = Relevant Association.

vegetable oil, refined carbohydrates and sweets, are suspected to be responsible for an increased risk of cancer (10). More difficult is to explain the mechanism by which over-weight and obesity appear protective of BC in premenopausal women. In this case obesity is not the cause but the secondary effect of hypoestrogenemia, since estrogens have a well-known influence on lipoprotein lipase gene expression in adipose tissue. Then hyperestrogenic women have less body fat than the hypoestrogenic ones. In premenopausal women obesity is then less depending upon dietetic factors (11). Furthermore, BCs that develop in obese premenopausal women are most often estrogen and progesterone receptor negative, consistent with the selection of non-estrogen-dependent tumor cells, which are instead dependent on growth factors such as insulin, insulin-like growth factor-I and some adipokines (13). Also the maintenance of a normal body weight, by diet and physical activity has been described as able to regulate growth factors and sex hormones binding globulin (SHGB) and to explicate protective effects (8). The relationship between obesity in childhood and adolescence and premenopausal cancer has been addressed

by many studies. A recent review analyzed forty-five peer-reviewed studies published in the last 30 years addressing this relationship (8). Twenty-two studies showed no direct relationship between obesity and BC. In contrast normal-weight adolescent are exposed to a higher risk of premenopausal cancer. The same review reported discordant results about effects of physical activity in childhood and teen years. Two studies showed a significant lower risk in women who had a background of athletic college activity. Five studies showed modest effects among women who had physical activity in their teen-age years and eleven studies showed no relation (8). The interpretation of these results requires a cautious approach, since contemporary teen-agers show a potentially harmful trend to obesity in a way unknown to previous generations. The reported studies investigated the dietary habits of mothers and grandmothers of present girls trusting their recall: it could be dangerous to infer the actual risk that obesity can represent for their granddaughters on this basis (16). Apart from body weight, also body size has been considered among a possible risk factor for BC with controversial results. In a study on 241 incidental BC cases and 481 controls in a black Caribbean population a positive association between body size and BC has been found while BMI was not. Body height was associated with BC in women 50 years of age and older (17). Since obesity is mostly due to an excessive caloric intake, some studies have evaluated the relationship between the energy intake and BC. Experimental studies shown the ability of caloric restriction of 30% and physical activity to modify, by different pathways, the expression of genes related to BC stem cells, the epithelial-mesenchymal transition and the growth and survival of BC cells (18). Nevertheless, in prospective studies it has been difficult to observe any influence between energy intake and BC, probably due to a short follow up. In the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial cohort, 29,170 postmenopausal women who successfully completed a food frequency questionnaire (FFQ) at entry (1993-2001) were followed, ascertaining 1,319 incidental BCs. Women in the highest quartile of energy intake had modestly, but significantly, increased BC risk (multivariate relative risk 1.21). More interesting is the results of an analysis of risk at different time of the follow up period. The relative risk, in fact, was 1.21 after 4 years from the first dietary assessment, but rose to 1.37 after 4 years and reached 1.55 at the end of the study (19). More recently a study on 3,298 British women, participating in the Avon Longitudinal Study of parents and children, showed that a higher caloric intake in childhood was related to an earlier menarche, with all the possible implications in terms of cancer risk, but this association was not confirmed after adjustment for body size (20).

6. DAIRY FOODS

The supposed relationship of milk and dairies high consumption with BC has been attributed to the content in growth factor and hormones of dairy products (21). Nevertheless, many large epidemiologic studies failed to demonstrate a relationship between dairy intake and BC (22, 23). Considering that the younger is the age of exposure, the higher is the chance of environmental factors to determine carcinogenesis, many studies examined the relationship between consumption of milk and dairies in the adolescence and subsequent development of cancer. Parodi has reviewed 3 cohort and 4 case control studies that evaluated the relative risk in 12 different associations (whole milk, fat milk, high fat, low fat and premenopausal or postmenopausal cancer). In 10 of these associations milk played a protective role, but only in 1 case the result was statistically significant (4). In two epidemiological studies Frazier *et al* (24,25) investigated the dietary habits of adolescent, observing an association between butter consumption or high fat milk and higher risk of BC, whereas low fat milk or vegetable fat and high dietary fiber showed a lower relative risk of cancer. Bessaoud *et al* (26) observed that adjusted OR (odds ratio) for dairy consumption between 134.3 and 271.2 g/day was 1.57 compared with the group with consumption lower than 134.3 g/day. However, the overall results were not consistent (26). Although a large part of the evidence seems favorable to a protective role, rather than a promoting one, many suspects have been raised concerning milk and dairies. Here it follows a summary of the mechanisms by which these nutrients might promote oncogenesis.

6.1. Estrogens content of milk and dairies.

Hartman *et al.* (27) in 1998 determined the content in estrone and estradiol in the German market basket and calculated that milk and dairies accounted for 60-80% of daily dose of estrogens, while eggs, meat and fish accounted for 10-20% each. A German woman assumes daily about 0.05 μg/day of estrogens from milk and derived products and 90% of this dose was constituted by estrone, a weak form of estrogen (27). The vast majority of these estrogens are inactivated by the liver. In the late follicular phase of the menstrual cycle a woman produces up to 1 mg /day of estradiol and 0,7 mg/day of estrone. In post menopause 40-200 μg /day of estrone are produced from androstenedione in adipose tissues, depending on body weight. Some authors then concluded that estrogens from milk and dairy couldn't explain a possible risk of BC (4).

6.2. Insulin- Like growth factor (IGF)

Insulin-like growth factor 1 (IGF1) is a peptide that stimulates mitosis, inhibits apoptosis and exerts its biological actions in both normal mammary gland and BC development. IGF1 circulates bound to proteins (IGFBP), one of which, IGFBP3, is particularly able to inhibits mitosis. The presence of IGFBP-proteases in tissues can free IGF-1 from binding proteins (4). Circulating IGF1 is positively associated with breast-cancer risk and the association is independent from IGFBP3 levels and from menopausal status (28). Some authors reported with highest value of IGF-1 increased risk principally in premenopausal women, however (4) the risk seems to be confined to estrogen-receptor positive tumors (28). IGF-1 and IGFBPs are produced in the liver under the control of growth hormon. It is estimated that in adults the liver and extra-hepatic tissues produce 10^7ng IGF-1/day. IGF-1 from saliva, biliary fluid, pancreatic juice and secretions from the intestinal mucosa, is estimated to total 380,000ng/day (4). Bovine milk

contains IGF-1, which has an identical amino acid sequence as the human IGF-1, and IGFBP-3. The level of both factors widely varies according with the period of lactation, parity of the cow and farm practice from a maximum level of 300ng/mL in colostrum to 7ng/mL at 1 week postpartum and eventually below 2ng/mL (29). Assuming a medium content of 4ng/mL and milk product consumption equivalent to 1.5 L milk/day Parodi (4) estimates that every day 6,000ng IGF-1 reach the gastrointestinal tract accounting for less than 0.06% of total daily IGF-1 production. Furthermore, this IGF-1 will undergo proteolysis during intestinal passage (4). Although supplementation of bovine colostrum is becoming a popular practice among athletes to improve performances because of its high level in growth factors and especially IGFs (30), feeding human adults up to 60g/d of a concentrated bovine colostrum protein powder for up to 8 weeks failed to show any increase in serum IGF-1 levels (31). Parodi concludes (4) that IGF-1 in dairy products is not implicated in the etiology of BC and athletes can continue to assume bovine colostrum even if it is not clear if it constitute a true advantage.

6.3. Lactoferrin

Lactoferrin is an iron binding glycoprotein present in milk and in other body fluids as blood, saliva, tears, bile, and pancreatic juice. This protein has antimicrobial, antiviral and antifungal activities. Because of all these positive properties, human recombinant lactoferrin and bovine lactoferrin are actually available on the market and are added to foods and clinical products. Aside to the direct antimicrobic, antiviral and antifungal action, lactoferrin is thought to exert an indirect effect by stimulating the mucosal immune function. One of the effects was attributed to the RNasic activity. Recent findings have suggested even a possible inhibitor effect on carcinogenesis (32).

6.4. Calcium

In the Malmo Diet and Cancer Study serum calcium was positively associated with BC in pre-menopausal women and in women with BMI>25 (33). Studies on Swedish Mammography Cohort do not support any association between calcium intake and BC risk (34). In a case control study based on 3,101 BC cases from the Ontario cancer registry and 3,471 random controls, no associations were found between overall vitamin D or calcium intake and BC risk (35). Abbas *et al* (36) support a protective effect of dietary vitamin D on premenopausal BC risk independent of dietary calcium intake. In a population-based case-control study in Germany, BC risk was significantly inversely associated with vitamin D intake. The OR and 95% CI for the highest intake category (>5 μg/day) was 0.50 (95% CI = 0.26-0.96) compared with the lowest (<2 μg/day; P_{trend} = 0.02). Regarding Calcium intake, no relationship was observed, with an OR = 0.73 (95% CI = 0.41-1.29) for the highest (>or = 1,300 mg/day) versus the lowest category (< 700 mg/day) P(trend) = 0.29). No statistically significant interaction between the two nutrients was observed (36).

7. FAT INTAKE

Fat intake has been studied under different respects. Fat are high caloric nutrients that include precursors of steroid hormones. These two factors have determined a potential strong association with the sex hormone concentrations and BC.In 2008 Shulz *et al* (6) reported the results of an evaluation of 15,351 women participants in the European Prospective Investigation into Cancer and Nutrition (EPIC)-Potsdam Study, among whom 137 incidental BCs were found. This study found a higher risk of BC in women with high fat diet irrespective of the type of fat and independent from the menopausal status (6).

Since fat are a very heterogeneous group of nutritional factors, some authors believe that there is inconsistent evidence on the direct relationship with BC (37). First of all, in order to examine the effects of dietary fat it is very important to distinguish between saturated, unsaturated, and particularly polyunsaturated fat. If we consider only saturated fat many studies have indicated a weak positive association between saturated fat intake and BC risk. This association was more pronounced for postmenopausal women who never used hormone therapy (38). A population-based, case-control study in the San Francisco Bay area, showed not only an increased risk of BC but also that the risk was increased for women cooking with hydrogenated fats rich in linoleic acid oil (vegetable or corn oil) compared to women using rich in oleic acid oil as olive oil (39). A positive association was also found for oleic acid but not for linoleic acid or saturated fat (39).

Polyunsaturated-fatty acids are instead considered protective factors. In experimental studies docosahexaenoic acid (DHA) has showed an anti-proliferative and anti metastatic effect, inducing apoptosis and reducing the invasive potential of cancer cells (40). A recent review suggest that DHA and rumenic acid, a naturally occurring isomer of conjugated linoleic acid (CLA), could improve BC treatment and outcome by an initial sensitization of residual tumor cells to chemotherapy and to radiation therapy (41). Also a prolonged rumenic acid supplementation can prevent then metastatic re-growth (41). In epidemiologic studies olive oil was inversely associated with BC risk (26, 39). Many other studies have failed to show any significant association between fats and BC. Hunter *et al* in 1996 published the results of a collaborative-pooled analysis of original data from large prospective studies conducted in seven independent populations from four countries (42). The study involved 4,980 cases from 335,000 women. Only one of these studies reported a positive relation between high levels of dietary fat and BC risk with a relative risk of 1,35 (43). The other six studies (3, 44-48) and the new pooled analysis found no positive association between total dietary fat intake and the incidence of BC (42). No differences were reported even considering different types of fat (saturated, monounsaturated, polyunsaturated, animal or vegetable fat). Reducing the energy intake from fat under 20% of total caloric intake was not able to reduce the risk of BC. On the contrary, reducing energy from fat to less than 15% of total energy intake has more than doubled the risk of BC (4). Only one study showed a small increase of risk in relation with higher consumption of cholesterol (42).

More recently a follow-up pooled analysis by Smith-Warner *et al.* (49) on 7,329 cases, confirmed the lack of association between total fat, fat class or animal or vegetable fat intake and the risk of BC. In addition, a study

on 3,846 US female nurses with BC, followed for at least 6 years or until death, showed a positive association between caloric and fat intake and mortality but, when results were fully adjusted for physical activity, the difference became not significant (50). Finally, although there are various reasons to avoid saturated fat and prefer unsaturated fat and especially olive oil, there is not enough evidence that BC should be one of these reasons.

8. MEAT

Five centuries after Falloppio beef meat is still investigated as being responsible for cancer. Various mechanisms have been proposed to justify this possible relationship, but results appear at least doubtful, probably because of the differences among samples. Taking into account just meat consumption, the results are inconsistent or at least show just a mild and doubtful increase in risk. In a review of ten case-control and cohort studies aimed to evaluate the association between meat consumption and BC in premenopausal women, the overall relative risk was 1.24, of which 7 case-control studies had a risk of 1.57 and 3 cohort studies had a relative risk of 1.11 (51). Only Bessaoud *et al* (26) in a case control study from southern France found that BC risk increased by 56% for each additional 100 g/day of meat consumption. A large study that includes the diet information from 319,826 women from EPIC, has been investigated the association of meat, egg and dairy consumption with BC. During the 8.8 years of median follow up 7,119 BC cases were observed. Although a modest increase in BC risk has been observed for high processed meat consumption or in countries in which meat is usually cooked at high temperature, no evidence has been found that meat; eggs or dairy intake is a risk factor for BC (23). Two cohort studies from Sweden did not confirm any relationship between red meat and the risk of developing BC. In the study on Swedish Mammography Cohort, a population-based cohort of 61,433 women, the dietary intake was assessed with the aim to estimate the relative risks for the association between long-term meat intake and BC. During a mean follow-up of 17.4 years, 2,952 incidental cases of invasive BC were ascertained. No association was found between total red meat, fresh red meat or processed meat intake and overall BC risk (52).

A contemporary cohort-study from Malmo on 11,699 postmenopausal women followed for more than 10 years found 430 cases of invasive BC. No statistically significant association was observed between cancer and type of meat (total amount, red, poultry, fish), even if a trend towards higher risk for red meat consumers was found. In addition, this study did not show any association with heterocyclic amine intake (53). When studies address the association between the method of cooking meat and BC some differences can be observed. Some Author relates this association to the content in heterocyclic amines (54-56), while some others attribute it generically to the high temperature and deep fried meat (57). The association with the expression of hormonal receptors appears inconsistent. The cited study by Larsson evidenced that the intake of pan-fried meat was positively associated with a risk of ER+/PR- tumors; the multivariate relative risk analysis for the highest compared with the lowest quartile of intake was 1.45 (52) suggesting that fried meat intake may increase the risk of ER+/PR- BC (52, 58) A population-based, case-control study (1,508 cases and 1,556 controls) on Long Island women supported the evidence that high temperature cooked meats can increase risk of BC. The risk was higher among lifetime consumers and especially among post-menopausal women and, particularly those with ER+PR+ neoplasm (56). A nested case control study among a cohort of 41,836 patients from the Iowa Women's Health Study showed a dose-response relationship between doneness levels of meat consumed and BC risk. Women who consumed hamburger, beef, steak and bacon well done to very well done had a 4.62 higher risk than women who consumed rare or medium done meats (55). A population-based case-control study from Shanghai that included 1459 cases of BC and 1556 matched controls showed an higher risk for women who used deep-fry red meat and fresh-water fish. Overweight was an additional risk factor for these women. Also, soybean oil, if not used for deep-frying, showed a protective effect (59). A case-control study from Montevideo on 365 BCs and 382 matched control cases hospitalized for non-neoplastic diseases showed an increased risk of BC for increasing intake of red meat, beef and fried meat, relating with the estimated intake of heterocyclic amines (60). The association could be explained also with the content in fat, but the results of the statistical adjustment suggested that heterocyclic amines, which carcinogenic potential is already well known, may explain the association observed between fried red meat and BC (60). White meat and boiled meat showed on the contrary a negative association (60). The protective effect of however cooked white meat was evidenced also in smaller sized case-control study from California that also failed to show any association with red meat (61). Even the content in acrylamide has been investigated. Acrylamide is formed in various kinds of foods during high temperature cooking and is considered a possible human carcinogen. A nested case control study on postmenopausal women from the Danish Diet, Cancer and Health Study has compared the level of acrylamide-hemoglobin in BC cases and matched controls. A 10-fold increase of the compound has been showed associated with a 2.7 increase of ER + BC (62).

Another mechanism by which red meat could increase the BC risk, unrelated to the type of cooking, can be related to the estrogens added to the bovine feeding, routinely done to improve the productivity of farms. This use is banned in European countries but it is not in USA. The hormones can pass into meat, milk and dairy and stimulate cancerogenesis in consumers (63). Also the content in iron has been related with a higher risk of BC. A study including 248 women with BC, 346 with fibrocystic disease and 1,040 controls selected from participants in a Breast Self Examination (BSE) trial in Shanghai, China, who accepted to answer a food frequency questionnaire and undergo to blood drawing for ferritine assessment, has shown a positive association between stored iron, dietary iron and BC. Stored iron, measured as ferritine levels, derives from red blood cells breakdown and is almost

independent from dietary intake. Chronic ferritine high levels could lead to development of fibrocystic disease while dietary iron may increase the risk of progression of these lesions to BC (64).

9. CARBOHYDRATES

A population based case control study on both pre and postmenopausal women (475 BC cases and 1,391 controls) showed that carbohydrate intake was positively associated with BC risk. Compared with women in the lowest quartile of total carbohydrate intake, the relative risk of BC for women in the highest quartile was 2.22 [95% confidence interval (95% CI) 1.63-3.04], adjusting for total energy and potential confounding variables. This association was present in premenopausal and postmenopausal women. Among carbohydrate components, the strongest associations were observed for sucrose and fructose. No association was observed with total fat intake (9, 65). Other more recent cohort and population-based case-control studies have confirmed this association principally for premenopausal women (66-68). Only one meta-analysis suggests that the association could be just apparent (69). The mechanism has been linked to the increased production of insulin after intake of carbohydrates. Insulin will bind to IGF-1- binding protein 1 and 2, leaving IGF-1 free. IGF-1 can promote cell proliferation and carcinogenesis (70-72). The higher the glycemic index of a nutrient, the higher will be the risk of its consumption, especially for postmenopausal women (70).

10. FIBER, FRUIT AND VEGETABLES

Fruit, vegetables and fiber have received the most attention since a controlled diet with low fat and high fiber content could be able to change the hormonal pattern. In fact, in a study on 291 women with a history of BC randomized in two groups, after 1 year the intervention group showed significant lower levels of estradiol without significant weigh loss compared to the control group (73).

Bessaoud *et al* (26) observed a significant lower relative risk of BC related to the higher consumption of raw vegetables. Comparing consumptions lower and higher than 101 g/day of raw fiber the OR for the group with higher consumption was 0.63. Kruk observed a protective effect of total vegetables, fruits, and vitamins intake over the risk of BC in both pre- and post-menopausal women (74). Similar protective effect has been showed in a prospective cohort study of 50,778 African- American women followed biennially for twelve years (75) while Cade *et al* (76) observed protective effects by fiber in premenopausal women. On the contrary, a pooled analysis of cohort studies conducted by Smith-Warner *et al* (49) suggested that this association is weak if present at all. The analysis included 7,377 incidental invasive BC cases occurring among 351,825 women whose diet was analyzed at baseline. Comparisons of the highest vs. lowest quartiles of intake showed a weak, non-significant association for total fruits (pooled multivariate RR, 0.93; 95% confidence interval [CI], 0.86-1.00; P for trend = .08), total vegetables (RR, 0.96; 95% CI, 0.89-1.04; P for trend = .54), and total fruits and vegetables (RR, 0.93; 95% CI, 0.86-1.00; P for trend = .12). No additional benefit was apparent in comparison to the highest and lowest deciles of intake. No associations were observed for green leafy vegetables, 8 botanical groups, and 17 specific fruits and vegetables (77).

In another very large prospective study conducted on 285,526 pre and postmenopausal women between from 8 European countries (EPIC study) no significant association between vegetable or fruit intake and BC was observed (78). In fact, evidence from epidemiological studies does not suggest a protective effect of dietary fibers (79, 80) although some specific foods are putatively able to significantly modify the risk pattern.

10.1. Cruciferous

Cruciferous vegetable are an especially rich source of glucosinolates, which may be converted by plants into myrosinase and by the gastrointestinal microflora to isothiocyanates, indole-3-carbinol, and other compounds believed to have anticancer properties. These agents may affect carcinogenesis through several mechanisms, including the induction of apoptosis (81) and a shift in estrogen metabolism to favor metabolites with lower estrogenic activity (82). In experimental studies benzyl isothiocyanate (BITC), a constituent of edible cruciferous vegetables, inhibits growth of human BC cells in culture and increases cytotoxicity of natural killer (NK) cells *in vitro* (81). In addition, isothiocyanates induce multiple phase II conjugating enzyme systems including glutathione S-transferases (GSTs), through nuclear transcription factor–E2–related factor 2–enhanced transcription. The overall effects of cruciferous vegetable intake appear to determine a reduction in systemic oxidative stress and a suppression of mutagenic and carcinogenic activity. Indeed, cruciferous vegetable intake has been inversely associated with the risk of lung, stomach, colorectal, bladder, and other cancers. However, despite strong biologic plausibility, the relation between cruciferous vegetable intake and BC risk is unclear, and several studies found no association between total cruciferous vegetable intake and BC risk (82). In contrast, a case-control study from Sweden (83), the United States (in premenopausal women) (84), and Shanghai (82) reported a reduction in BC risk associated with cruciferous vegetable intake. A study by Terry did not show a relation between total fruit and vegetable consumption and BC risk. However, consumption of Brassicacea vegetables was inversely associated with BC risk. Dividing the data more finely, the relative risk (RR) among women in the highest decile (10%) of brassicacea vegetable consumption (median, 1.5 servings per day) compared with the lowest decile (virtually no consumption) had a RR of 0.58 (83). The case-control study by Ambrosone *et al.* (84) was specifically designed to examine associations between diet and BC. He found that the consumption of cruciferous vegetables, particularly broccoli, was associated with a reduced risk of premenopausal BC. Since some differences could be explained by different genotypes, Lee *et al.* (82) found that a greater intake of cruciferous vegetables with higher isothiocyanate content was associated with lower postmenopausal BC risk. In addition, he found that the *GSTP1 Val/Val* genotype was associated with a greater BC

risk, and premenopausal BC risk was attenuated among women with a high cruciferous vegetable intake. This may suggest that a genetic predisposition to BC related to *GSTP1* genotype could be modified by cruciferous vegetable intake (82). In a large study, 2,048 cases of BC and 1,969 controls were analyzed for deletion polymorphism in genes GSTM1 and GSTT1 and a base transition polymorphism at codon 105 (Ile-->Val) in GSTP. Results of this study did not show any substantial risk of BC for carriers of a single gene GST polymorphisms (85).

10.2. Grapefruit

Since grapefruit inhibits cytochrome P450 3A4 and may affect estrogen metabolism, its role in the carcinogenesis of BC was investigated in the EPIC study. However no direct relationship between grapefruit consumption and BC protection has been found (86).

10.3. Phytoestrogens

Phytoestrogens are plant derived compounds found in a wide variety of foods and includes isoflavonoids - such as genistein and daidzein mostly present in soy, lignans - from almost all kind of vegetables but principally in flax seeds and cereals and coumestans, from beans and mostly from clover sprouts. Actually the asserted beneficial effects of phytoestrogens - including a lowered risk of osteoporosis, heart disease, BC, and menopausal symptoms - have led to a large consume as dietary supplements (87).

10.3.1. Soy and isoflavones

As for other nutrients, the epidemiologic evidence has preceded the experimental and clinical studies (88). Asiatic women share a low risk of BC that increase when they migrate in Western countries or adopted a western lifestyle (89). However, the significance of this interaction is not clear, so that in 2006 a workshop concluded that there is not enough evidence on the effects of soy foods or isoflavones on BC in high-risk women and on the survival of BC patients. It was also recommended to study the potential impact of soy foods on BC in this population by examining cancer risk markers (e.g., cell proliferation, apoptosis) using breast tissue samples obtained via random periareolar FNA or ultrasound-guided biopsies (90). Indeed, recent experimental studies on breast samples from esthetic reducing surgery, showed that an implementation of diet with soy flavonoids results in a higher presence of these substances having estrogen-like or antiestrogenic activity in the breast tissue (91). A meta-analysis including 6 cohort and 12 case–control studies, found a small reduction in the risk for BC, stronger for premenopausal women (92). Asian women whose soy intake was high during puberty experienced lower risk for BC than women who did not consume soy products or did it only as adults (89). In a study on 268 BC cases, early life soy intake was associated with lower ER+ and PCNA staining but an adverse effect on proliferation markers was excluded (93). Results of similar investigation on women participant in the EPIC-Norfolk (244 cases, 941 controls) showed no association between phytoestrogens intake and BC (94). It is likely that isoflavones act by different mechanisms such as inhibition of cell cycle, induction of apoptosis and promotion of differentiation, as observed in breast cell culture studies. *In vitro* and *in vivo* isoflavones at high doses have shown ability to inhibit angiogenesis, invasion and metastasis. At physiological concentrations isoflavones stimulate antioxidant enzymes and enhance detoxification and DNA repair (89). Various mechanism and pathways are involved in thus process, from steroid hormones and estrogen receptor (95) to the modulation of EGF, IGF-1, MAPK, Akt and PPARγ (89).

The involvement of IGF-1 has been showed also in a randomized double blind study, in which healthy men consumed 40g of soy protein or milk protein daily for 3 months. Serum IGF-1 levels increased with both protein sources, but were significantly higher only for soy protein. This report should induce to certain cautiousness in the regards of these substances (96).

10.3.2. Lignans

Lignans are polyphenolic compounds derived from phenyalanine. Whole grain seeds (flax, sesame, rye etc), fruits (apricot, strawberry, peach), brassicacea vegetables, olive oil and a great list of vegetables are rich in lignans. Also red wine and black tea are sources of lignans, but flax seeds are the richest (97). Intestinal bacteria are able to transform the plant lignans matairesinol and secoisolariciresinol in enterodiol and enterolacton, respectively, which have a weak estrogenic and antiestrogenic activity (98). In western diet these phytoestrogens are more widespread and more present than isoflavonoids (98) and are thought to have a protective effect against breast and prostate cancer. This putative property has been suggested with regard to their ability, supported by experimental data, to compete with type II estrogen receptor, to induce sex hormone binding globulin (SHBG), to inhibit placental aromatase and to act as antioxidants (99). Study on mice supplemented with phytoestrogens suggested that enterolactone has powerful antiestrogenic effects on BC growth by downregulating angiogenic factors derived both from the stroma and the cancer cells, whereas dietary genistein does not have any antiestrogenic effects (100). In spite of these interesting theoretical and experimental premises, epidemiologic studies are not consistent. A large cohort study from Dutch women of EPIC showed no beneficial effect from isoflavones and lignans (98) while a study on postmenopausal French women showed a reduced risk of ER- and PR- BC (101). Only the study on the Swedish Mammography Cohort showed a risk of BC significantly lower for women in the higher quartile of lignan intake (17%) (102). Furthermore a survival study found that higher lignan intake was associated with a statistically significant reduction in the risk of all cause of mortality and a significantly reduced risk of BC mortality among postmenopausal women (103).

10.3.3. Coumestans

Coumestans, among which the most important is coumesterol, are the least studied among phytoestrogens but the most estrogen-like and for this reason are considered potentially harmful. We found just one study specifically addressing coumestrol intake. This study on a Swedish cohort showed a decreased risk for women with

intermediate consumption of this phytoestrogen, but this result need to be confirmed for the lacking of dose response effect and for the low consumption observed. The same study did not show any association between isoflavonoids and BC (104).

11. VITAMIN AND OTHER SUBSTANCES

Although vitamins are usually thought to be beneficial, except for some experimental studies, no protective effect against BC has been proven.

11.1. Vitamins

Vitamin E, Alpha tocopherol, and its isoforms have shown some effectiveness in the prevention of BC in some studies on experimental cancers (105) but not in human BC (106, 107). In the EPIC population study overall dietary intake of β-carotene, vitamin C and E was not related to BC risk either in pre- or in postmenopausal women. However, in subgroups of postmenopausal women assuming replacement hormones, a weak protective effect of β-carotene and vitamin E from food cannot be excluded (106). In the Swedish mammography Cohort some beneficial effects have been showed among smokers and among women who do not use dietary supplements (107). Folate, vitamin B6, vitamin B12, methionine, choline, and betaine are nutrients involved in one-carbon metabolism. Some large studies have addressed the issue of association between intake of these nutrients and BC, but the overall results are inconsistent. Indeed, the Nurses' Health Study II on 90,663 premenopausal women did not show any association between vitamin supplementation and the prevention of BC (108). Another study on 35,032 post-menopausal women, among whom 743 were diagnosed with BC, showed that high intake of folates may have a protective effect particularly against ER- BC. Multivitamin use can attenuate the risk associated with alcohol drinking (109). Quite different is the conclusion by Stevens *et al.* (110) that, in a prospective cohort study on 70,656 postmenopausal women, of whom 3,898 developed BC, observed that the highest quintile of dietary folate intake was associated with slightly higher, although not statistically significant, risk of BC. No association was found for total folate, vitamin B-6, or vitamin B-12, while methionine was inversely associated with BC risk. Furthermore, the association of dietary folate with BC was not modified by other nutrients or alcohol. Also a multiethnic study on dietary carotenoids, retinols, vitamin C and tocopherols has failed to show any meaningful association (80). Also Vitamin D antiproliferative effects have been suggested to be effective against BC, particularly in hormone-receptor-positive cells. Few epidemiologic studies have investigated the association between vitamin D and hormone-receptor-defined BC, and the results are conflicting. In a study by Blackmore *et al.* (111) though an increased intake of vitamin D (from the sun and diet) was most consistently associated with a significantly reduced risk of ER+/PR+ tumors, comparable non-significant associations were found for receptor-negative (ER-/PR-) tumors. This study suggested that vitamin D is associated with a reduced risk of BC regardless of ER/PR status of the tumor. More recently a nested case-control design within the Malmo Diet and Cancer Study compared 764 BC cases with 764 matched controls. The study showed a weak, non-significant inverse association between BC risk and 25OHD (33). In the aforementioned study Anderson *et al.* (35) found that Vitamin D from supplements was independently associated with reduced BC risk. Finally, a study on 777 premenopausal and 787 postmenopausal women showed a higher breast density in premenopausal women who were currently using multivitamin supplement. This could be a risk factor for cancer. No enhancement in breast density was observed in postmenopausal women (112).

11.2. Choline

Recognized as an essential nutrient, choline is largely present in many foods, especially meats and egg. Choline takes part to a wide range of metabolic processes and its deficit can produce liver diseases, atherosclerosis and neurologic disorders (113). Utilizing the cohort of the Long Island Breast Cancer Study Project (LIBCSP), a nested case-control study on 1,508 cases and 1,556 controls investigated the associations of dietary intake of choline and two related micronutrients, methionine and betaine, and the risk of BC. The highest quintile of choline consumption was associated with a lower risk of BC [odds ratio (OR): 0.76] compared with the lowest quintile. The study suggests that choline metabolism may play an important role in BC etiology. A subsequent study on the same cohort showed a significant reduction in mortality associated with choline intake (114, 115).

12. OLIGOELEMENTS

Many oligoelements that may be present in foods, water, workplace and environment can contribute to development of BC. In particular, cadmium, chrome and zinc have been associated with the development of BC (116). Selenium is an essential trace element with antioxidative, antimutagenic, antiviral and anticarcinogenic properties, and its activity is explained by its interaction with other elements (As, Cu, Ni, Co, Cr, Mn, Zn, Cd, Sn, Pb, Hg, Bi, Mo, Ag, Au, etc.) . The sequestration of elements by selenium represents an efficient natural detoxification mechanism for some of these elements, but also results in the physiological inactivation of selenium. [116] Thus, selenium acts as cofactor for various antioxidant enzymes and its presence in the toenails has showed to be related to a protective effect against DNA damage after gamma-irradiation in BRCA1 mutation carriers, decreasing the number of chromosome breaks (117). The aliment richest in selenium is pork meat. Other good sources are wholegrain products, legumes, milk, seafood, fish and meat (118). Although the available case-control study are small sized, there is increasing evidence that the dietary selenium intakes are still too low in many countries and that supplementation of selenium could reduce both the incidence and the mortality for cancer (116, 118).

13. ALCOHOL

Alcohol is the only factor among the dietary elements that has been clearly shown in epidemiological

studies to increase the risk of developing BC (4, 7, 119). Sonestedt*et al.* (53) basing on the results of a cohort study on 11,699 postmenopausal women, reported a significant dose related increased risk of developing BC - in alcohol drinking women. Analyses on a random sample of subjects from California teachers Study confirmed the observation of increased BC risk associated with greater alcohol consumption, and this was the sole dietary factor associated with overall BC risk in this study (120). With a median caloric intake of 1,525 Kcal/day, consumption of about 30 g/day (20 g/1000Kcal) of alcohol per day was associated with a relative risk of 1,36, compared with the median intake of 0.9g/day (120). A nested case-control study on 560 French -Canadian women, none carrier of BRCA, 280 with BC and 280 not affected, showed an increased risk for BC with a daily intake of 9 g of alcohol, regardless of its type (wine, beer, other spirits) (121). However, these results are not unanimous. Indeed, a study conducted on 90,663 premenopausal women followed for 12 years and whose dietary intake had been assessed by questioners three times during the follow up, failed to show any influence of vitamin or alcohol intake on the overall risk of developing BC, even for ER - cancers (108). Furthermore, a study on hereditary cancer showed that moderate drinking determines a reduction in the risk among BRCA1 but not among BRCA2 carriers (122). Many mechanisms have been suggested to explain the association between alcohol and carcinogenesis. Alcohol dehydrogenases, present in many tissues including breast, converts alcohol in acetaldehyde, whose mutagenic action is well known (123, 124). Ethanol can also increase the conversion of steroid in estrogen by aromatases and some study observed an increased concentration of estrogen in the plasma of postmenopausal women with moderate consumption of alcohol (123, 125). Even an induction of mutations in the oncosuppressor gene BRCA1 has been described. Among the suggested mechanisms, the oxidative stress by induction of cytochrome P450 2E1, the accumulation of iron, the induction of DNA hypomethylation, the increased production of inhibitory guanine nucleotide regulatory proteins and protein kinase, and the impairment of retinoic acid metabolism worth a mention (125, 126). Besides, alcohol induces various other events: it can inhibit the expression of E-cadherin, a tumor suppressor that contrast the loss of adhesion of cells and the ability to metastasize and stimulate the expression of metalloproteases 2 and 9, even in this case promoting invasion and metastases. Finally an EGFR mediated pathway even for moderate consumption of alcohol has been postulated (123).

IGF1 could be an additional mediator, since IGF1 concentrations, adjusted for age, were higher in moderately overweight women and in moderate alcohol consumers than in other women (28).

14. DIETARY PATTERNS AND BREAST DENSITY

Some authors investigated the relationship between dietary pattern and breast density on mammography, which is considered a risk factor for BC. In a study from the Minnesota Breast Cancer Family study among 1,286 women with breast density estimates, no significant evidence for associations of dietary patterns with breast density was found. But in stratified analysis the fruit-vegetable-cereal and salad-sauce-pasta/grain patterns were inversely associated with percent breast density among current smokers (127). A case control study from multiethnic population of Hawaii found a slight positive association between fat and meat and breast density (128). A second study on 157 high-risk women found a strong relationship of high-protein diet and high breast density. The relationship was significative only for women with strong familiar risk but without known cancer syndromes (129). Martin *et al.* recently reported data from a prolonged follow up of their previous study (130) in which the assumed association of low fat diet and lower breast density is not confirmed. They examined the patients who were premenopausal at entry and changed status during follow up, suggesting that the potential protective effect of low fat diet against BC is not mediated by a reduced breast density (131).

15. STUDIES ON SURVIVAL

Pierce, in a recent review of two large observational studies - Women's Intervention Nutrition Study and Women's Healthy Eating and Living (WHEL) - did not observe a real impact of diet in improving prognosis for postmenopausal women with early stage BC. However, it is possible that some subgroup could have some benefit from changing diet pattern. Particularly, a specific examination of results from WHEL suggests that the dietary intervention reduced distal recurrences among the subgroup without hot flashes at baseline (132). Nevertheless, a prospective study performed on 1,490 women diagnosed and treated for early-stage BC showed that a healthy life style was associated with longer survival. The combination of consuming five or more daily servings of vegetables-fruits, and accumulating 540 or more metabolic equivalent tasks/wk (equivalent to walking 30 minutes 6 d/wk), was associated with an approximate 50% reduction in risk. Among those who adhered to this healthy lifestyle, there was no apparent effect of obesity on survival. The effect was stronger in women who had hormone receptor-positive cancers (133). In a large, population-based cohort study of 5,042 female BC survivors in China, soy food intake, as measured by either soy protein or soy isoflavone intake, was inversely associated with mortality and recurrence. The hazard ratio associated with the highest quartile of soy protein intake was 0.71 (95% confidence interval [CI], 0.54-0.92) for total mortality and 0.68 (95% CI, 0.54-0.87) for recurrence compared with the lowest quartile of intake, regardless of Estrogen receptor status and of Tamoxifen administration (134). Some authors suggest that the better survival previously thought to be related to a better nutritional regimen is probably due to a lowering of non-breast-cancer mortality (135), nevertheless women with BC should abstain from alcohol and consume a diet lower in total and saturated fat, higher in vegetables and fiber, which results in a mild to modest weight loss (136) . Indeed, BC has now a higher survival rate than before and women with cancer have to prevent now the collateral effects of treatment and treatment-related weight gain and sedentary behavior (135).

16. CONCLUSION

After all, we can conclude that the only useful advice for women who want to fight BC with a primary prevention, once excluded a family risk, is just to abstain from alcohol and control their weight, also with the help of physical exercise. Every other dietetic restriction or integration will be pointless, even if some supplements like vitamin D have been linked with lower risk. Nevertheless, avoiding certain nutrients, such as saturated fats and simple carbohydrates, and improving the overall quality of diet can be helpful in lowering the co-morbidities and the other causes of mortality in BC survivors.

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