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Role of dietary patterns in the prevention and regression of insulin resistance-related cancers

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Abstract. In the last years plant-based diets have been regarded as beneficial for the prevention of widely spread diseases, such as cancer. On the opposite, frequent ingestion of animal products, enriched in proteins and fats, and often causative of decreased insulin sensitivity, higher serum cholesterol and insulin like growth factor (IGF)-1 levels and increased abdominal obesity, is often directly associated to the risk of several cancer types, such as colorectal, breast and prostate cancers, all known to be linked to insulin resistance. Here, the role of plant vs animal-based diets in the prevention and regression of insulin resistance-related cancers is discussed. Despite some divergences, overall the reported studies suggest that plant-based dietetic regimens might be protective against these types of cancers, opposite to animal-based dietary patterns. Additionally, as the cooking process normally alter the availability of phytonutrients and determine the formation of several food toxins, the possible beneficial effect associated to the consumption of raw plant-derived vs cooked foods is discussed.

Keywords: Plant-derived foods, animal-derived foods, prostate cancer, breast cancer, colorectal cancers, raw food

1. Introduction

Diet, physical activity and life style play crucial roles in determining the risk to develop cancer, especially during oldness. Particularly, several studies have recently investigated the role of plant-based diets in the prevention of cancer-related diseases. However, some of these studies might look contradictory; this contradiction arises from the fact that often vegetarian dietetic patterns are very different, accounting for semi-vegetarian regimens, (including plant foods, dairy products, eggs and fish), lacto-ovo vegetarian diets (with plant foods, dairy products and eggs) and vegan diets (based on plant foods only). Moreover, even the simple consideration that vegetarian/vegan consumers normally adopt a more restricted (i.e. less abundant) dietetic habit, is a positive aspect for the prevention of cancer and chronic-degenerative diseases, commonly affecting western or recently economically developed societies. Even though several influential nutritional bodies have been advising on the positive effects associated to vegetarian and vegan dietetic regimens [1, 2], data coming from epidemiological and meta-analysis studies are not always in agreement with respect to the actual protective effects linked to the preferential consumption of plant-derived foods.

For instance, a meta-analysis of several prospective studies showed no significant differences in the mortality caused by colorectal, stomach, lung, prostate or breast cancers and stroke between vegetarians and "health-conscious" non-vegetarians [3]. Authors of this study suggest that vegetarians normally show a decreased mortality rate for ischemic

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heart disease, which is probably due to the observed lower total serum cholesterol levels, the lower prevalence of obesity and the higher consumption of antioxidants, typically found in fruits, nuts and vegetables. According to their conclusions, the large consumption of fruits and vegetables, rather than the exclusion of meat products, might be the key factor accounting for the high prevalence of healthy vegetarians [3].

Another meta-analysis investigated cardiovascular disease mortality and cancer incidence among vegetarians and non-vegetarians. These data showed that all-cause mortality was 9% lower in vegetarians than in non-vegetarians and, particularly, vegetarians had a significantly lower overall cancer incidence (18%) than non-vegetarians [4].

In another work, data from 5 prospective studies were combined to compare the death rates related to common diseases of vegetarians (i.e. people eating neither meat nor fish), with those of non-vegetarians with similar lifestyles. While, the mortality rate for ischemic heart disease was 24% lower in vegetarians than in non-vegetarians, apparently there were no significant differences in mortality for cerebrovascular disease, stomach cancer, colorectal cancer, lung cancer, breast cancer, prostate cancer or all other causes combined, between vegetarians and non-vegetarians [5].

Low-fat vegan diets may be especially protective in regard to cancers linked to insulin resistance, such as breast, colon and prostate cancer; conversely, the high insulin growth factor (IGF)-1 activity associated with heavy ingestion of animal products may be largely responsible for the epidemic cancer burden. Undoubtedly, in vegetarians and vegans the lower total serum cholesterol levels, the lower prevalence of obesity and the higher consumption of antioxidants and phytochemicals are clear-cut protective factors from the incidence of metabolic-related diseases and cancers [6, 7].

Additionally, also the beneficial role of raw, rather than cooked, plant-food consumption, has been acknowledged as a possible component of healthy (vegetarian) diets. In this regard, a recent study, addressing the correlation existing between fruit and vegetable consumption and mortality rate within the "European Prospective Investigation Into Cancer and Nutrition" (EPIC), evidenced a stronger inverse association for raw than for cooked vegetable consumption in the prevention of cancer death [8].

In the next paragraphs I will discuss the scientific evidences supporting the protective role of plant derived vs animal derived food consumption for the prevention of colorectal (i), breast (ii) and prostate (iii) cancer, all linked to insulin resistance, and the possible further beneficial role of raw plant-derived food consumption (iv).

1.1. Animal-derived vs plant-derived food consumption and the risk for colorectal adenoma and colorectal cancer

Several studies suggested that meat products consumption, particularly cured red meat, opposite to plant-derived products, is strongly associated with a higher incidence of colorectal cancer (Fig. 1). Particularly, some recent meta-analyses showed that high consumers of cured meats and red meat have an increased risk of colorectal cancer; particularly, beef meat and cured pork meat have been found to promote colon carcinogenesis in rats [9]. Authors proposed that dietary calcium and α-tocopherol reduced the pro-carcinogenic effects elicited by cooked, nitrite-treated and oxidized high-heme cured meat in rats, and this was also confirmed by a study in volunteers [10].

In another study it has been shown that the consumption of fried, preserved and grilled meat, animal fats, sugar and overweight are positively associated with colorectal polyps, opposite to the consumption of fruits, vegetables, rye- and brown bread, green tea, yogurt, garlic, boiled food, mineral water, but also fish, lamb and hare, which seem to have a strong protective effect against large bowel polyps. The authors proposed that particularly vegetarian food, plant oil, rural life, legumes, fish, fruit and vegetable consumption might represent protective factors for the prevention of colorectal cancer [11].

A parallel study from Millen AE and co-workers screened for colorectal cancer 3.057 cases with at least one prevalent histologically verified adenoma of the distal large bowel with 29.413 control subjects [12]. They observed an inverse association between colorectal adenoma, a precursor of colorectal cancer, and total fruit intake, regardless of adenoma histopathology and multiplicity, even though this protective effect was seen only for colon, and not rectal, adenoma. Particularly, diets enriched in fruits and deep-yellow vegetables, dark-green vegetables, onions and garlic resulted modestly associated with reduced colorectal adenoma risk [12].

A previous study analyzed the effects of dietary consumption of cholesterol, fibre (vegetables, fruits, beans and grains), and macronutrients (protein, carbohydrate and fat) on risk for colorectal adenomas in a cohort of 236 subjects with histologically confirmed adenomas and 409 adenoma-free control subjects [13]. Authors found that carbohydrate

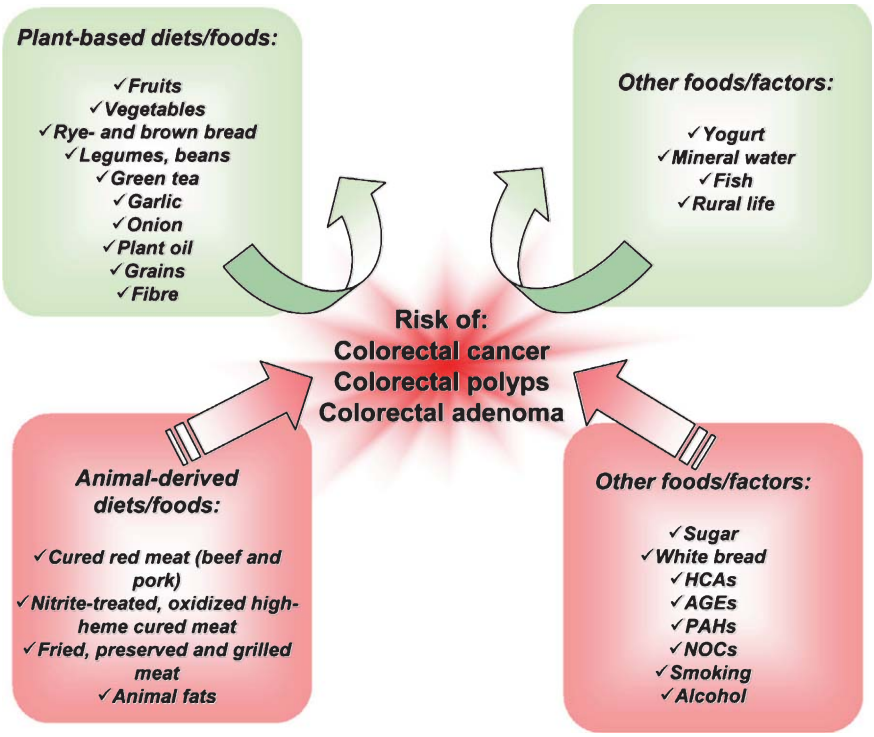

Fig. 1. Dietary patterns, foods and other factors in relation to the risk of colorectal cancer. Plant-based diets and foods and also fish are commonly associated to a decreased risk of colorectal cancer and colorectal adenoma (upper quadrants with curved arrows), opposite to animal-derived products, refined sugars and cooked meat-derived toxicants (lower quadrants with straight arrows).

intake was inversely associated with adenoma risk in women. The intake of plant-derived fruit and of fibre was also inversely related to adenomas in women. On the opposite, total fat consumption showed a positive association in women, with comparable results for saturated fat intake. Curiously, risk rates in men were generally similar, although not statistically significant. These data support the hypothesis that a diet high in fat and low in carbohydrates, fruits and fibre, increases the risk not only for colorectal cancer but also for precursor colorectal adenomas [13].

With regard to vegetarian diets, a recent study examined the protective effect of a vegetarian diet against colorectal adenoma and advanced adenoma among Buddhist priests in Korea, who are obligatory vegetarians, compared to age and sex-matched controls. Non-vegetarian diets were shown to significantly increase the prevalence of colorectal and advanced adenoma compared with the vegetarian diet [14]. Analogously, a British study measured the incidence of colorectal cancer in a cohort of 10.998 men and women, and found a positive association between cancer risk and smoking, alcohol and white bread consumption, opposite to frequent consumption of fruit [15].

There are several potential mechanisms directly relating red meat consumption to cancer, including the intake and the formation of polycyclic aromatic hydrocarbons, heterocyclic amines, N-nitroso compounds and heme iron [16]. In particular, the endogenous formation of N-nitroso-compounds (NOCs) is mediated by red meat consumption and is strongly associated to colorectal cancer induction. In this regard, Lewin MH and colleagues conducted an epidemiological study on some volunteers, who were asked to eat a high (420 g) red meat dose, or to eat vegetarian meals or high-fibre diets for 15 days in a randomized crossover design while living in a volunteer suite, where food was carefully controlled and all specimens were collected. In 21 volunteers, there was a consistent and significant increase in endogenous formation of NOCs with the red meat diet compared with the vegetarian diet, as measured by apparent total NOCs in feces [17].

On the opposite, the intake of fruit and vegetables seems to lower the risk of colon cancer; plant-based diets, by providing high amounts of selenium, folic acid, vitamin D, chlorophyll and antioxidants, such as flavonoids and

carotenoids, seem to contribute to this effect [18]. In particular, flavonoids are known to have a protective effect from colorectal cancer. Indeed, flavonoids have scavenging effects on activated carcinogens and mutagens, affecting cell cycle progression and altering gene expression and protein stability, as shown in HCT-116 colon cancer cells [19]. However, epidemiologic studies on flavonoid intake and colorectal cancer risk often provided inconsistent results, with positive, inverse and/or null associations, making any public health recommendations in this regard a little premature at this time [20–22]. Rather than pointing to the specific role of single nutrients, it might be the overall quality of the diet to play a protective role against colon cancer.

1.2. Animal-derived vs plant-derived food consumption and the risk for breast cancer

It is known that breast cancer rates are low in many Asian populations and it has been widely suggested that diets low in animal product and high in soy food consumption may reduce the risk rate for this type of neoplasm (as summarized in Fig. 2). However, findings from epidemiological studies are sometimes equivocal. These controversies showing either null or positively weak associations between diet and breast cancer, might derive from measurement errors, timing of dietary exposure and differences according to cancer characteristics or diet-gene interactions [23]. Furthermore, the most established risk factors for breast cancer are, so far, obesity and alcohol consumption. General preventive recommendations, besides pointing to a reduction of alcohol consumption, include a decrease of red meat and total dietary fat intake, together with an increase in vegetable and fruit consumption [24]. Increasing the consumption of plant-derived foods might be of great relevance especially if alcohol is consumed on a regular basis. However, the consumption of animal products *per se* does not seem to clearly increase breast cancer risk [25].

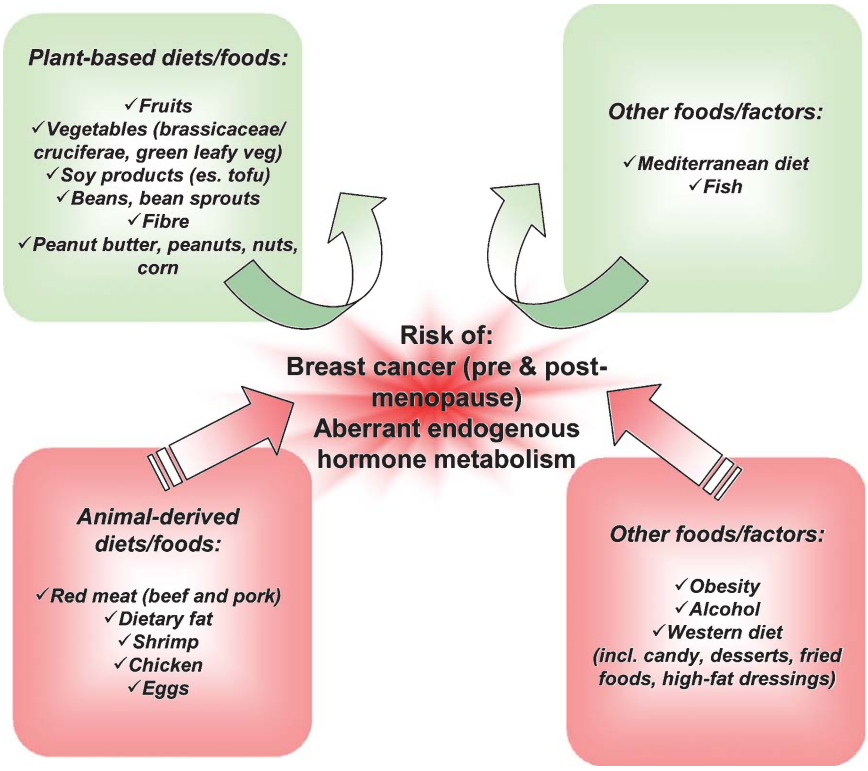

Fig. 2. Dietary patterns, foods and other factors in relation to the risk of breast cancer. Plant-based diets, plant foods and also fish are commonly associated to a lower risk of breast cancer, contributing to the physiological regulation of the hormonal milieu (upper quadrants with curved arrows). On the opposite, animal derivatives, obesity and alcohol consumption are strongly associated to an increased breast cancer risk (lower quadrants with straight arrows).

Importantly, studies addressing the effects of long-term overall diet compositions might be highly informative to understand the relevance of dietetic habits in the determination of breast cancer risk. A study conducted on 37.643 British women participating in the EPIC, investigated the relationships between a vegetarian diet and isoflavone intake with breast cancer risk. Nevertheless, authors of this study did not find a significant association between vegetarian diets or dietary isoflavone intake and the risk for breast cancer [26]. Oppositely, another study conducted on postmenopausal Asian women showed a positive correlation between western diet and increased breast cancer risk. Authors described two dietary patterns: a "vegetable-soy" pattern (with high consumption of tofu, cauliflowers, beans, bean sprouts and green leafy vegetables) and a "meat-sweet" pattern (including shrimp, chicken, beef, pork, candy and desserts). In adjusted unconditional logistic regression analyses, the risk to develop breast cancer was not associated with the vegetable-soy pattern, but with the meat-sweet pattern, only in postmenopausal women, and specifically in those with estrogen receptor-positive cancers, indicating that a western diet might increase the risk of breast cancer [27].

A recent study compared different dietary patterns and their relation to breast cancer risk in a large cohort of Californian women (California Teachers Study), diagnosed for invasive breast cancer between 1995 and 2009. Five predominant dietary patterns were described: a plant-based diet (high in fruits and vegetables), a high-protein-fat diet (high in meats, eggs, fried foods and high-fat dressings), a high-carbohydrate diet (high in convenience foods, pasta and bread products), an ethnic diet (high in legumes, soy-based foods, rice and dark-green leafy vegetables) and a salad-wine diet (high in lettuce, fish, wine, low-fat salad dressing, coffee and tea). Data indicate that the plant-based diet was associated with a lower breast cancer risk, especially for estrogen receptor-negative - progesterone receptor-negative tumors. Additionally, the salad-wine pattern was associated with an increased risk of estrogen receptor-positive - progesterone receptor-positive tumors and this effect was slightly attenuated after adjustment for alcohol consumption [28].

Several studies tried to address the possible effects of nutritional intervention strategies (i.e. cancer diets) in postmenopausal women and/or in patients diagnosed for breast cancer. One of these studies assessed the effects of a change in dietary composition on endogenous hormone metabolism in postmenopausal women, with the aim to examine whether this intervention could favourably modify insulin sensitivity, IGF-1 and IGF-binding proteins (IGFBPs) levels, and total and bioavailable testosterone and estradiol, which would be expected to reduce breast cancer risk. The dietary intervention consisted in reducing the intake of total fat and refined carbohydrates, increasing the n-3 / n-6 saturated fatty acid ratio, and increasing intakes of foods rich in dietary fibre and phytoestrogens. Importantly, women of the "intervention group" showed a significant reduction of waist circumference, body weight, fasting serum levels of testosterone, C peptide, glucose and insulin area after glucose tolerance test, and a significant increase of serum levels of sex hormone binding globulin (SHBG), IGFBP-1, -2 and growth hormone-binding protein, whilst serum levels of IGF-1 did not change. Authors concluded that this dietary intervention strategy seems to be relevant to induce changes in endogenous hormone metabolism that might reduce the risk to develop breast cancer [29].

Another nutritional intervention trial in women previously treated for breast cancer, showed that increased intake of cruciferous vegetables, such as broccoli and cabbage, especially when consumed as raw, resulted protective against breast cancer recurrence [30]. Analogously, a more recent trial from the same group conducted on 3.080 breast cancer survivors undergoing tamoxifen treatment (the Women's Healthy Eating and Living (WHEL) Study), reported that increased cruciferous vegetable consumption, was associated with a reduced risk of breast cancer recurrence [31].

Regarding the specific role of certain plant subcategories, brassica vegetables, like broccoli, cauliflower and cabbage, seem to promote a reduced breast cancer risk [25]. A recent systematic review highlighted that the Mediterranean dietary pattern in particular, together with diets composed mainly of vegetables, fruit, soy, enriched in phytoestrogens, and also fish, seem to be associated with a lowered breast cancer risk [32].

Amongst plant-derived nutrients, dietary fibre could reduce the risk of breast cancer by modulating the enterohepatic circulation of estrogens. A recent study showed that vegetarian postmenopausal women without breast cancer presented a lower fat/fibre ratio, a higher intake of total and cereal fibre (g/d)/body weight (kg), a significantly lower level of plasma estrone-sulfate, estradiol, free-estradiol, free-testosterone and ring-D-oxygenated estrogens, and a significantly higher level of SHBG, opposite to breast cancer subjects, indicating that the fat/fibre ratio might be useful in evaluating dietary effects on estrogen metabolism [33].

Accordingly, data from the EPIC, accounting for a total of 11.576 invasive breast cancer cases, showed that breast cancer risk was inversely associated with the intake of total dietary fibre and vegetable-derived fibre, but not with

fruit, cereal or legume-derived fibres. For vegetable fibre, strong association was recorded for estrogen receptor-negative and progesterone receptor-negative than for estrogen receptor-positive and progesterone receptor-positive tumors [34].

Another recent study investigated whether specifically vegetable-derived protein and fat, included in diets reported during pre-adolescence and adolescence, were associated with subsequent risk for benign breast disease (BBD) in young women (The Growing Up Today Study). Vegetable fat's and protein's greatest sources were peanut butter, peanuts, nuts, beans (i.e. beans, lentils and soybeans) and corn. Importantly, a daily serving of anyone of these foods, particularly of peanut butter and nuts at the age of 11 and 14 years, was associated with lower risk of BBD. Additionally, girls with a family history of breast cancer, showed a significant lower risk of BBD as young women, when consuming these foods or vegetable fat [35]. In conclusion, all these studies suggest that early consumption of plant-derived foods might prevent the risk to develop breast cancer both in pre and post-menopausal age (Fig. 2).

1.3. Animal-derived vs plant-derived food consumption and the risk for prostate cancer

Alike for colorectal and breast cancers, also prostate cancer risk has been linked to specific dietetic patterns (Fig. 3). Epidemiological studies highlighted a positive association between dietary fat (particularly saturated, animal fats, n-6 fatty acids), meat (especially when fried and grilled) and dairy products and the risk to develop prostate cancer. Oppositely, dietary intake of plant foods, such as cereals, soy, fruit and carotenoid-enriched vegetables seem to prevent and ameliorate prostate disorders [36]. In particular, legume-based vegetarian diets, enriched in flavonoids, such as phytoestrogens, have been found to play a protective role for prostate cancer [37]. This was confirmed by *in vitro*

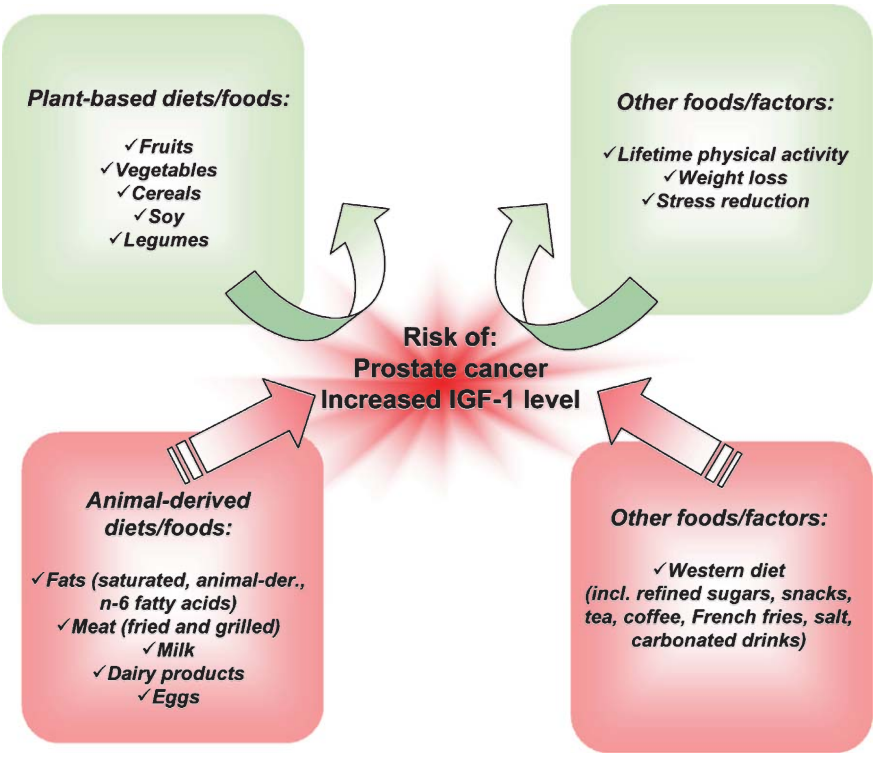

Fig. 3. Dietary patterns, foods and other factors in relation to the risk of prostate cancer. Plant-based diets, plant foods, physical activity and reduction of body weight (especially of abdominal obesity) are associated to a lower risk of prostate cancer and a reduced IGF-1 serum level (upper quadrants with curved arrows). Conversely, dairy products, animal fats and meat increase prostate cancer risk (lower quadrants with straight arrows).

studies assessing the effects of individual or combined mixtures of several phytoestrogens, such as genistein, quercetin and biochanin-A, on prostate cancer cells [38]. Particularly, combined, rather than individual phytochemicals, seem to elicit cancer preventive effects.

A case control study compared several factors, such as the dietary intake, the consumption of lycopene rich food and lifetime physical activity, confronting prostate cancer subjects (cases) with control subjects (controls), matched for age and ethnicity. Interestingly, cases showed a significantly higher intake of fat and a lower intake of fruits, vegetables (particularly, tomatoes, watermelon, guava, pomelo, papaya, mango, oranges, dragon fruit, carrot) and lycopene, as compared to controls. Additionally, not practicing any physical activities at the age of 45–54 years, was associated with a three-fold increased risk to develop prostate cancer [39].

Another recent study investigated the relationship between the consumption of vegetables, alpha- and beta-carotene and the risk of prostate cancer in a Japanese cohort, accounting for 15.471 Japanese men, of which 143 were affected by prostate cancer. Data indicated that vegetable and beta-carotene intakes were both not associated with the risk of prostate cancer, opposite to alpha-carotene, which was found preventive against this cancer type [40].

An Iranian study assessed the relationship between two different dietetic patterns (i.e. "western" and "healthy") and the risk to develop prostate cancer. The western diet was high in refined sugars, meat, snacks, tea, coffee, French fries, salt, carbonated drinks, red or processed meat; the healthy diet included high amounts of legumes, fruits, fruit juice, vegetables, boiled potatoes, whole cereals and also, fish, dairy products and eggs. Interestingly, while the healthy pattern was only marginally related to decreased risk of prostate cancer, the western pattern was positively associated to the prostate cancer risk [41]. It should be noticed that in this specific study, the so called healthy pattern included dairy products and eggs, which are known to elevate the risk of prostate cancer, especially when ingested at high quantity [42, 36].

Several recent prospective trials have investigated whether various dietary and lifestyle interventions could lower the risk for prostate cancer. One of these studies, in particular, assessed whether a very low-fat vegan diet (i.e. 12% fat kcals, with various supplements and lifestyle changes), a traditional low-fat diet (i.e. 25% fat kcals with flaxseed supplementation) and a low-glycemic index diet could possibly reduce prostate cancer risk [43]. The low-glycemic index and the very low-fat vegan diets were found to induce epigenetic changes of tumor gene expression and these effects were possibly associated with the observed weight loss. Oppositely, the traditional low-fat diet did not elicit any effect [43]. This is in accordance with other epidemiologic and preclinical investigations, suggesting that cholesterol intake and serum cholesterol levels may be linked with the development and progression of prostate cancer [44].

Additionally, a 6-month pilot intervention trial sought to determine whether adoption of a plant-based diet, together with stress reduction, could reduce the increase in expression level of the prostate-specific antigen (PSA), known to be a disease progression marker, in asymptomatic, hormonally untreated patients, who were undergoing a consistent increase of PSA following surgery or radiation [45]. Anthropometric and haematological measurements showed a reduction in the waist-to-hip ratio and an increase in circulating SHBG, together with a decrease of the PSA increasing rate especially from 0 to 3 months. This suggests that the adoption of a plant-based diet and stress reduction may be effective in reducing central adiposity and improving the hormonal milieu in patients with recurrent prostate cancer [45]. Accordingly, plant-based diets might also help for the improvement of survival and tertiary treatment following prostate cancer diagnosis [46].

Conversely, a study on an EPIC cohort accounting for 150.000 men recruited in the 1990 s in eight European countries, assessed the relationship of prostate cancer risk with dietary intake and with blood-related markers of nutritional factors. Data indicated that there was no direct correlation between prostate cancer risk and the intake of meat, fish, fruit, vegetables, fibre, fat, alcohol or with blood levels of fatty acids, carotenoids, tocopherols, B vitamins, vitamin D or selenium. However, men with a high intake of protein, especially from dairy products, and high blood levels of IGF-1 displayed a higher prostate cancer risk factor [47].

Furthermore, it has been noticed an association between single nucleotide polymorphisms (SNPs) and the circulating concentrations of IGF-1 and IGF binding protein 3 (IGFBP-3) [48]. A recent study investigated the possible association between 16 SNPs, linked to circulating IGF-1 or IGFBP-3 concentrations, and the risk of prostate cancer, within subgroups defined according to dietary protein intake. Data indicated that total, animal, dairy and plant-derived protein intakes were positively associated with circulating IGF-1 levels, but not with IGFBP-3 and/or the risk of prostate cancer [49].

Despite these sometimes controversial studies, accumulating evidence shows that consuming milk or dairy products may contribute to the risk of prostate cancer [50], but also ovarian cancers, autoimmune diseases and some childhood disorders [51, 16]. This is currently a widely debated topic as, while some authors keep on recommending three daily servings of milk products in order to prevent the risk of low bone mass [52], others declare that milk is not necessary for humans after weaning, that the nutrients it contains, such as calcium, are readily available in plant foods, such as sesame seeds, and that well-balanced vegetarian diets should not include milk and other dairy products to prevent chronic diseases [51].

1.4. The beneficial effects associated with the consumption of raw plant-derived foods

Nowadays, raw plant-derived food consumption, commonly named "raw veganism", is drawing a great interest. The cooking process normally changes the availability of some nutrients, such as phytonutrients, vitamins and minerals, promotes the destruction of digestive enzymes and alters the structure and digestibility of food. For these reasons, raw food consumption has been correlated to reduced risk of cancer [53, 54, 8] (Fig. 4). A meta-analysis of scientific studies conducted from 1994 to 2004 showed an inverse correlation between the risk of developing certain types of cancer and eating both raw and cooked plant foods. However, raw vegetable consumption tended to be associated with decreased cancer risk somewhat more often than consumption of cooked vegetables, and this was possibly due to the fact that in cooked vegetables, the availability of anti-cancer nutrients and bioactive compounds is normally lower than in raw vegetables [53]. Moreover, another study showed significant benefits in reducing breast cancer risk when large amounts of raw vegetables were included in the diet; authors attributed some of these effects to the higher concentration of phytonutrients that get normally destroyed during the cooking process [55].

A recent work analyzed the phenolic composition comparing raw and processed (i.e. boiled or germinated) dark beans and the neuroprotective and anti-cancer effects of their respective extracts. Data showed that the content of phenols, especially anthocyanins, was higher in raw than in processed beans, and, even though both extract types decreased reactive oxygen species release and induced cytotoxicity on cancer cell lines, raw beans displayed the highest neuroprotective and anti-tumoral effect. Authors also commented that cooked dark beans resulted more digestible due to their higher absorption at intestinal level, while maintaining their protective anti-oxidant effects at cellular level [56].

Another study evaluated the effect of three common cooking practices (i.e. boiling, microwaving and steaming) on the biological activities of three types of Brassicaceae (i.e. broccoli, cauliflowers and Brussels sprouts) on HT-29 human colon carcinoma cell line. The highest anti-proliferative and antioxidant activities were displayed by the fresh vegetable extracts in this order: broccoli > cauliflowers = Brussels sprouts. Moreover, even though the three cooking methods influenced the anti-proliferative activity of these extracts, they didn't considerably alter their antioxidant properties [57].

Furthermore, lentils (Lens culinaris L) contain several bioactive compounds that might be preventive against cancer. An interesting study assessed whether the culinary thermal treatment affected lentils chemopreventive

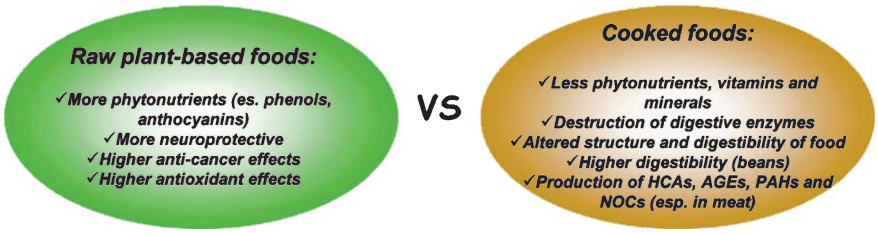

Fig. 4. Summary of the properties and the effects of raw-plant versus cooked foods. Raw plant-foods are highly enriched in antioxidants, vitamins and minerals, possibly contributing to reduce cancer-related risk and neurodegeneration. On the opposite, cooked/processed foods in general result to be poor in micronutrients and by cooking meat at high temperature several food toxicants get normally produced, such as HCAs, AGEs, PAHs and NOCs, known to promote carcinogenesis.

potential *in vivo*. To this end, 4–5 week old male rats were fed for five weeks with either raw whole lentils (RWL), raw split lentils (RSL), cooked whole lentils (CWL) or cooked split lentils (CSL). Raw soybeans (RSB, Glycine max), which are known for their chemopreventive effects, were used as comparison control. At the end all rats received two subcutaneous injections of the carcinogen azoxymethane (15 mg/kg, once a week for 2 consecutive weeks). Data indicated that total aberrant crypt foci number was lower for RSB, CWL and RSL in comparison with the CSL group, and hepatic glutathione-S-transferases activities resulted increased in rats fed with all treatment diets when compared with control (C) diet. These data suggest that consumption of lentils might be protective against colon carcinogenesis and that the cooking process, at least in this animal model, possibly improved the chemopreventive potential of whole lentils [58].

Moreover, the potential associations between intake of raw vs cooked cruciferous vegetables and survival among bladder cancer patients was tested on 239 bladder cancer patients along an average of 8 years follow up. In particular, raw broccoli consumption was found to be inversely associated to bladder cancer mortality, while no significant associations were found for total vegetables, total fruits or other individual cruciferous vegetables [59].

Moreover, it has been extensively described that the cooking process can promote the formation of several toxic substances, especially coming from cooked meat and fish products. Since the 1990 s, several works described the formation of heterocyclic amines (HCAs) coming from cooked muscle meat [60, 61]; high rates of HCAs can cause cancer in animals and possibly also in human beings [62]. Researchers of the National Cancer Institute showed that cooking meat below 100 °C creates "negligible amounts" of HCAs and also microwaving meat before cooking may substantially reduce HCA production [63].

Nevertheless, a frequent use of microwave should not be encouraged, as microwaving has been shown to highly decrease all studied antioxidants in broccoli, compared to other cooking methods [64]. Additionally, re-heating refrigerated breast milk before use using the microwave significantly reduced the anti-infective factors in human milk [65]. Additionally, also nitrosamines get formed by cooking meat products and by preserving them in salt and smoking, and nitrosamines have been linked to colon and stomach cancer [66, 67]. Moreover, the cooking process also generates heat-created toxins, known as AGEs (i.e. advanced glycation end products). Many cell types, such as endothelial cells, smooth muscle cells, cells of the immune system, lung, liver, kidney or peripheral blood cells bear the receptor for AGEs (named RAGE) that, when binding AGEs, contributes to age and diabetes-related chronic inflammatory diseases [68, 69] and also cancer [70]. In this regard, a recent study reported that specific RAGE gene polymorphisms seem to be correlated to the development of breast cancer [71].

Finally, also polycyclic aromatic hydrocarbons (PAHs) are toxins known to promote carcinogenesis [72, 73] and get produced by the cooking process particularly of beef, pork, fish, or poultry, especially when using high-temperature methods, such as pan frying or grilling directly over an open flame. Both HCAs and PAHs can damage the DNA when they get metabolized by specific enzymes (bioactivation). Several studies have found that the activity of these enzymes, which can differ among people, may determine different cancer risk levels associated with exposure to these compounds [74, 75].

These studies globally suggest that phytonutrients availability and food toxicants formation are both related with the cooking process (Fig. 4), which can possibly contribute to cancer occurrence in humans.

2. Discussion

In the last years plant-based diets have been regarded as beneficial for the prevention of widely spread diseases, such as cancer [1, 2]. It has been noted that rather than not eating meat, it is the consumption of high amounts of vegetables and fruits to play a distinct role in the prevention and the regression of these diseases [3]. However, the frequent ingestion of animal products is also responsible of producing high IGF-1 activity, which is known to be associated to prostate cancer [47]. Also, the lower level of total serum cholesterol and the lower prevalence of obesity in vegetarians and vegans, who normally consume higher amounts of plant foods enriched in antioxidants and phytochemicals, are also protective factors from the incidence of these diseases [6, 7]. For this reason, a "precautionary principle" also to food choices is currently recommended in order to prevent cancer risk [76]. In particular, the following "precautions" should be adopted: limiting/avoiding alcohol, dairy products, red and processed meat and meat cooked at high temperature, whilst increasing the consumption of soy products, fruits and vegetables [76].

In the present work the role of plant vs animal-based diets have been discussed in correlation to the risk for insulin resistance-related cancers, such as colon, breast and prostate cancers. The reported studies globally indicate that plant-based dietetic regimens result to be preventive against these types of cancers, whilst animal-based dietary patterns, based on consumption of meat, dairy products and eggs, seem to increase cancer risk. Additionally, it should be pointed out that often epidemiological studies on vegetarian nutrition-related topics show sometimes discrepancies, which are possibly due to the fact that vegetarian/vegan diets are often very different, including different amounts and types of fruits and vegetables, which can be consumed raw or heat-processed, different timing of analysis, different types of condiments/dressings used to flavour and process foods, etc... For this reason, it would be more appropriate to refer to "descriptive subtypes" of vegetarian diets, rather than broadly talking about the "vegetarian" dietary category [77].

Furthermore, as the cooking process alters the availability of anti-oxidants and anti-cancer compounds, such as flavonoids, vitamins and minerals, consumption of raw plant foods, rather than cooked, is considered a further beneficial factor for cancer prevention [8, 78], given also the reduced production of food toxicants, such as HCAs, AGEs, PAHs and NOCs. However, the use of specific cancer diets, such as raw plant diet, which are often followed by cancer patients, should be done with great care, in order to avoid possible nutritional deficiencies [79].

Conflict of interest

The author has no conflict of interests.

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