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Breast cancer prevention in premenopausal women: role of the Mediterranean diet and its components

Daniela Laudisio[1], Luigi Barrea[1]*, Giovanna Muscogiuri[1], Giuseppe Annunziata[2], Annamaria Colao[1] and Silvia Savastano[1]

[1]*Dipartimento di Medicina Clinica e Chirurgia, Unit of Endocrinology, Federico II University Medical School of Naples, Via Sergio Pansini 5, 80131 Naples, Italy*

[2]*Department of Pharmacy, University of Naples 'Federico II', Italy; Via Domenico Montesano, 49, 80131 Naples, Italy*

Abstract

Breast cancer (BC) is a growing public health concern in most developed and developing countries. Since an increasing number of patients with BC are diagnosed before the menopause and premenopausal women show a more aggressive phenotype, there is consistent interest in promoting prevention strategies in order to reduce the incidence of BC in the premenopause. The Mediterranean diet (MD) has been reported to have beneficial effect in terms of cancer prevention. This healthy dietary pattern consists primarily of foods having important antioxidant properties along with a favourable fatty acid profile, all associated with a reduced risk of cancer. Due to the large variability in study subject characteristics, the protective role of the MD on BC still remains controversial and studies that have investigated the association between adherence to the MD and risk of BC in premenopausal women are fewer than those in postmenopausal women. In addition, the possibility that the beneficial effects of the MD are due to a single component or might more probably derive from the synergic effects of all components of the MD remains a scantly explored field. Considering the increased risk of recurrence and mortality rate of BC in premenopausal women as compared with postmenopausal women, the aim of the present report is to provide a general overview of the current evidence on the relationship between BC and the MD specifically in premenopausal women, and to emphasise the potential role of the MD as an effective measure to reduce the risk of developing BC in premenopausal women.

Key words: **Breast cancer: Premenopausal women: Mediterranean diet: Nutrients**

Introduction

Breast cancer (BC) is a growing public health problem. Despite the current efforts in preventing BC, its incidence is increasing in most developed and developing countries[1–4]. Approximately 1·4 million new cases of BC are diagnosed worldwide each year, with a mortality rate of about 450 000 per year[5]. The risk factors for BC include age, genetic mutations (BRCA1 and BRCA2)[6], younger age at menarche, nulliparity, first pregnancy after the age of 30 years, older age at menopause, dense breast tissue[7], hormone replacement therapy, use of oral contraceptives[8] and personal and family history of BC or other breast diseases[9]. In this complex scenario, it is of fundamental importance to evaluate accurately the role of modifiable risk factors, such as nutrition. Although BC is generally considered an age-dependent disease, nearly 7 % of BC is diagnosed in premenopausal women under 40 years of age[10], while another 3 and 0·65 % concern women less than 35 years and less than 30 years of age, respectively[11–14]. Although with some discrepancies, BC in premenopausal women is generally more aggressive than in postmenopausal women, showing higher histological grading, increased proliferation rate, higher rates of vascular invasion[15], and a higher proportion of triple-negative BC[9]. Consistently, the presence of an extensive intraductal component as adjunctive risk factor for BC recurrence in premenopausal women has been associated with an increased risk of recurrence and mortality rate compared with postmenopausal women[16,17]. Furthermore, hormone treatment seems to be significantly less efficacious in premenopausal women and the presence in BC of endocrine receptors, including oestrogen receptors (ERα, ERβ) and progesterone receptor (PR), human epidermal growth factor receptor 2 (HER-2) and proliferation markers are significantly different in women ≤ 45 years compared with those ≥ 65 years of age[18]. The incidence of BC among premenopausal women is increasing[19] and represents a significant issue in developing countries because more than 20 % of BC cases and more than 20 % of deaths occur in women aged 45 years, in contrast to developed countries where these figures correspond to less than 12 % and 10 %, respectively[19,20]. This increase in BC among premenopausal women is not exclusively attributable to an increase in life expectancy, but rather to several environmental

Abbreviations: BC, breast cancer; COX, cyclo-oxygenase; ER, oestrogen receptor; HER-2, human epidermal growth factor receptor 2; HR, hazard ratio; HT, 3,4-dihydroxyphenylethanol; IGF, insulin growth factor; MD, Mediterranean diet; OL, oleuropein; PR, progesterone receptor; ROS, reactive oxygen species; RR, relative risk; WCRF, World Cancer Research Fund.

* **Corresponding author:** Dr Luigi Barrea, fax +39 081 746 3668, email luigi.barrea@unina.it

risk factors and unhealthy lifestyles, such as unbalanced diets, lack of exercise and use of alcohol and tobacco[21]. The World Cancer Research Fund (WCRF) in 2018 reported that choosing healthier lifestyles could prevent 4 million cases of cancer around the world[22,23], 30 % of which by simply adopting healthy dietary habits[24]. Notwithstanding the benefits of single nutrients, the dietary pattern as a whole may allow us to better capture the complex inter-relationships between dietary components and represents a more adequate approach toward understanding the relationship between diet and cancer[25]. Despite cancer prevention through dietary and lifestyle choices having been identified as a future cancer research priority[26], evidence on a specific healthy dietary pattern, such as the Mediterranean diet (MD), is limited and weak[23]. In particular, no consistent pattern of association between the MD and BC in both pre- and postmenopausal women emerged in the WCRF report. However, the vast majority of the studies included in this report were conducted in non-Mediterranean settings, where a high variability in the compliance with the MD is very likely, and were not specifically conducted in premenopausal women. Thus, the relationship of the MD with BC in premenopausal women still remains an open issue. The aims of the present report are to provide a general overview of the updated evidence on the association of BC and adherence to the MD specifically in premenopausal women, and to emphasise the potential role of the MD and its principal components as an effective measure in the prevention of BC in premenopausal women.

The Mediterranean diet

Although limited by a large variability in study subject characteristics, type and length of interventions, selected end-points and statistical analysis, several epidemiological and clinical studies strongly support the association between nutritional factors and the development or progression of cancer, including BC[27–30]. As is it well known, the MD has long been considered as the utmost example of a healthy, well-balanced diet. The term 'Mediterranean diet' was originally coined by Ancel Keys, but its definitions may vary across different settings and it is actually difficult to describe in detail a Mediterranean dietary pattern and its components. Indeed, there are many different 'Mediterranean diets', based on cultural, ethnical, religious and economical differences existing among the various populations and countries situated along the Mediterranean basin[31]. However, different MD models do generally share some important characteristics; specifically, they all have an abundant plant-based food content, such as fruits and vegetables, whole grains, legumes and nuts, including olive oil as the main source of monounsaturated fats; they are all characterised by a limited intake of red and processed meat, saturated fat and refined sugars, low-to-moderate intake of low-fat dairy products and moderate consumption of fish, while a regular, but moderate, alcohol (mostly red wine) consumption with meals is emphasised[32,33]. The main components of a MD, such as fruits and vegetables, fibres, olive oil, fish and red wine, are rich sources of several bioactive compounds, including antioxidants (i.e. carotenoids, flavonoids, resveratrol and other polyphenolic compounds)[34,35] and *n*-3 PUFA. In summary, a Mediterranean dietary pattern tends towards a moderate content in total fats (32–35 % of total energy), a relatively low content in saturated fat (9–10 % of total energy), a relatively high quantity of fibres (27–37 g/d) and *n*-3 PUFA[36]. This type of diet has been widely studied and several studies have reported a protective effect against various chronic diseases and cancers, including BC[37] and the MD may well be identified as a promising approach for preventing BC[38]. Besides the potential role exerted by the anti-inflammatory properties of food antioxidants on overall incidence of cancer, more specifically BC[39], Carruba *et al.*[40] illustrated that a traditional MD in healthy postmenopausal women may reduce the risk of developing BC also because of its effects on the metabolism of endogenous oestrogens. Adherence to the MD has been extensively evaluated by different standardised indexes[41–43]. However, there is no objective method to measure MD adherence, nor are there commonly accepted criteria to evaluate the indexes[44]. To date, one of the most frequently used is the MD score proposed by Trichopoulou *et al.*[45,46]. This index is based on nine dietary components and the method consists of assigning a value of 0 or 1 to each component, depending or food groups and on food servings per meal, day, and week, with a median as cut-off point. In particular, for components typical of the MD (i.e. fruits and nuts, vegetables, legumes, cereals, fish and seafood, high monounsaturated:saturated dietary lipid ratio, mainly olive oil, and regular but moderate intake of ethanol, red wine) is attributed a value of 1 for an intake greater or equal to the sex-specific median, while a value of 0 is attributed in case of intake lower than the median. Conversely, for components that are not typical of the MD (namely red meats), a value of 1 or 0 is given for a consumption less or more than the sex-specific median, respectively. Thus, the total MD score ranges from 0 (minimal adherence to the traditional MD) to 9 (maximal adherence)[46].

Data sources and searches

A literature search was performed using the electronic databases PubMed (August 2018) and Scopus (August 2018). The search strategy for PubMed was: ('Mediterranean diet' or 'Mediterranean' or 'diet' or 'dietary pattern' or 'dietary adherence') and ('breast cancer') and ('prospective' or 'follow-up' or 'cohort' or 'longitudinal') and ('premenopausal women'). The search strategy had language restrictions; only the documents in English have been taken into consideration. Moreover, reference lists from reviews, meta-analyses and the retrieved articles were searched to identify further relevant studies. The literature search was conducted by one author (D. L.), with questions or uncertainties resolved by discussion with another author (S. S.). Cohort studies and case–control studies investigating the association between the MD and risk of BC incidence in the premenopausal female population were selected.

Breast cancer in premenopausal women and the Mediterranean diet: cohort studies and case–control studies

Studies that have investigated the association between adherence to the MD and risk of BC in premenopausal women are

fewer than those in postmenopausal women[23]. It should also be considered that, although postmenopausal women are at a higher risk for BC development than younger women, BC during pre-menopause seems to be more aggressive than in postmenopause. Some of the epidemiological evidence available suggested that a MD could reduce the risk of BC[34,38]. As mentioned above, an inconsistent pattern of association between the MD and BC in both pre- and postmenopausal women emerged in the more recent WCRF report[23]. Of interest, considering the strict relationship between the MD, BMI and glucose metabolism on one side[47–49], and BMI and BC on the other side[50], the association between the MD and BC remained significant also after adjusting or stratifying data for common confounding variables, including BMI and body fatness. However, the association between the MD and BC is more evident for postmenopausal women than in premenopausal women. In fact, for premenopausal women the results are still conflicting[23]. Nevertheless, other studies that considered specific cancer subgroups defined by hormone receptor status[34,51–53] or menopausal status did not confirm such observation[54–56]. Trichopoulou *et al.*[38] evaluated in a cohort study the relationship between conformity and adherence to an MD and BC risk within the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort in Greece[38]. The sample population used for this analysis consisted of 14 807 women, of which 240 with incident BC, with a follow-up period of approximately 9 years. Increasing conformity to the MD was not associated with a lower BC risk in the entire cohort (hazard ratio (HR) 0·88 for every 2 points; 95 % CI 0·75, 1·03) or in premenopausal women (HR 1·01 for every 2 points; 95 % CI 0·80, 1·28), but there was a marginally significant inverse association among postmenopausal women (HR 0·78 for every 2 points; 95 % CI 0·62, 0·98; *P* for interaction by menopausal status = 0·05). However, in this study menopausal status was ascertained at enrolment and not at the time of diagnosis of cancer, which is likely to have introduced some sort of misclassification[38]. In a cohort study, Cade *et al.*[56] evaluated the risk of developing BC associated with consumption of two common dietary patterns: a Mediterranean dietary pattern and a dietary pattern conforming to the WHO Healthy Diet Index; the study population included 828 incident cases of BC in 33 731 women, with a mean follow-up of 9 years[56]. The compliance to the diet was assessed at baseline using a 219-item self-administered FFQ. This study evidenced that in premenopausal, but not postmenopausal, women, there was a not significant inverse association with an increasing adherence to the MD pattern, but the maximal adherence to the MD was associated with a HR of 0·65 (95 % CI 0·42, 1·02; $P_{trend} = 0·09$) compared with minimal adherence. Although based on a large sample size, the results of this study were limited by the fact that lifestyle questionnaires were self-filled by the participants in the study[56]. In another cohort study, Couto *et al.*[54] investigated the association between the MD and BC risk in pre- and postmenopausal women, aged 30–49 years, within a span of 16 years[54]. Adherence to the MD pattern was not associated with an overall decrease in BC risk or with specific BC characteristics in both pre- and postmenopausal women. However, women that reported a higher adherence to the MD also presented higher risk factors for BC (family history of BC, use of oral contraceptives or postmenopausal hormone therapy, higher alcohol consumption), which might have probably counteracted the beneficial effect of the MD[54]. In another prospective cohort study, Buckland *et al.*[34] evaluated the association between adherence to the MD and risk of BC among 335 062 women recruited from 1992 to 2000 in ten European countries, and followed for 11 years on average[34]. Adherence to the MD was assessed using a semi-quantitative FFQ administered through a personal interview. The results showed that a higher adherence to the MD was associated with a lower risk of BC in postmenopausal women only, mainly in ER^-/PR^- tumours, while this association was not consistent in premenopausal women. However, the results of this study should be interpreted with caution as a similar weight was given to each component and the foods, with the assumption that they have equivalent effects on BC risk. Similarly, a meta-analysis of only cohort studies by van den Brandt & Schulpen[51] focusing on postmenopausal BC did not show a significant inverse association between overall postmenopausal BC and high adherence to the MD, although the HR estimate of 0·94 was marginally significant. A very recent meta-analysis on primary prevention of overall cancer risk including eighty-three studies indicated an inverse association of adherence to the MD with cancer mortality and risk of BC among postmenopausal women, but not among premenopausal women (pooled relative risk (RR) 1·3)[57].

In a case–control study, Castello *et al.*[58] evaluated the association between dietary patterns and risk of BC in Spanish women, stratifying the sample by menopausal status and tumour subtype. The authors recruited 1017 incident BC cases and 1017 matched healthy controls without a history of BC[58]. Cases and controls completed a structured questionnaire collecting information on demographic and anthropometric measurements, personal and family history, past physical activity and diet and menopausal status. In this study three food models were considered: the Western pattern, characterised by high intakes of fatty and sugary products and red and processed meat; the prudent pattern, characterised by high intakes of low-fat dairy products, vegetables, fruits, whole grains and juices; Mediterranean dietary patterns. Adherence to the Western dietary pattern was associated with a higher risk of BC (OR for the top *v.* the bottom quartile 1·46; 95 % CI 1·06, 2·01; $P = 0·02$), especially in premenopausal women (OR 1·75; 95 % CI 1·14, 2·67; $P = 0·01$). Conversely, the Mediterranean pattern was associated with a lower risk of BC (OR 4th *v.* 1st quartile 0·56; 95 % CI 0·40, 0·79; $P < 0·01$). Although the detrimental effect of the Western pattern was equally observed in all tumour subtypes, the protective effect of the Mediterranean pattern was stronger for triple-negative BC (OR 0·32; 95 % CI 0·15, 0·66; $P = 0·04$). Finally, no association was found between adherence to the prudent pattern and the BC risk[58]. Subsequently a multicase–control study by Castello *et al.*[59] confirmed these data. The objective of this study was to externally validate the effect of the three food models on BC risk, as reported in a previous study (EpiGEICAM study)[59]. A high adherence to the Western diet resulted in an increased BC risk in both postmenopausal women (OR 4th *v.*1st quartile 1·48; 95 % CI 1·07, 2·05; $OR_{1SD\text{-}increase}$ 1·14; 95 % CI 1·01, 1·29) and premenopausal women (OR 4th *v.* 1st quartile 1·68; 95 % CI 1·02, 2·79; $OR_{1SD\text{-}increase}$ 1·19; 95 % CI 1·02, 1·40), while a greater

adherence to the Mediterranean pattern seemed to afford protection only in postmenopausal women, although this protective effect did not reach statistical significance[59]. Another case–control study by Murtaugh *et al.*[60] evaluating the associations of dietary patterns (Western, prudent, Native Mexican, Mediterranean, and dieter) with risk for BC confirmed a significant protective role of the MD on incidence of BC in both Hispanic and non-Hispanic women. These cases had a histologically confirmed diagnosis for either *in situ* or invasive BC. Controls were healthy women frequency-matched for ethnicity, BMI and menopausal status. Food intake was reported by using a computerised, interviewer-administered dietary history questionnaire[60]. The Western and prudent dietary patterns were associated with greater risk of BC (OR 4th *v.* 1st quartile 1·32; 95 % CI 1·04, 168; $P < 0·01$; OR 4th *v.* 1st quartile 1·42; 95 % CI 1·14, 1·77; $P < 0·01$), and the Native Mexican and MD patterns were associated with lower risk of BC (OR 4th *v.* 1st quartile 0·68; 95 % CI 0·55, 0·85; $P < 0·01$; OR 4th *v.* 1st quartile 0·76; 95 % CI 0·63, 0·92; $P < 0·01$)[60]. In a very recent study, Turati *et al.*[61] investigated the association between adherence to the MD and BC risk in a case–control study conducted in Italy and Switzerland. This analysis included 3034 BC cases and 3392 controls. Information on dietary habits before diagnosis (for cases) or hospital admission (for controls) was based on a validated and reproducible FFQ, and conformity to the traditional MD was assessed through MD score. The Mediterranean dietary pattern was associated with a reduced risk of BC. In particular, women with the highest level of adherence to the MD reported an approximately 20 % decrease in risk compared with women with the lowest adherence. As far as the MD score is concerned, a score of 0–3 was associated with OR for BC of 0·86 (95 % CI 0·76, 0·98), 0·82 for a MD score of 4–5 (95 % CI 0·71, 0·95) and 0·95 for a MD score of 6–9 (95 CI % 0·92, 0·99) with a significant downward trend of BC risk ($P = 0·008$). The exclusion of the alcohol component from the MD score did not materially modify the OR (OR 0·81; 95 % CI 0·70, 0·95, for MD score ≥ 6). Of interest, pre- and postmenopausal women reported almost the same results[61]. Although encouraging, the global examination of these results on the protective effect of the MD on BC still remains controversial, as reported in Table 1, and did not shed light upon the possibility that the beneficial effects are due to a single component or to the synergic effects of all components of the MD.

Table 1. Characteristics of cohort studies and case–control studies, of breast cancer (BC) incidence and adherence to the Mediterranean diet (MD), in premenopausal and postmenopausal women

Author	Experimental design	Country	Follow-up (years)	Enrolled subjects (*n*)	Age of enrolment (years)	Incident BC cases	Menopausal status	BC incidence	Methods
Trichopoulou *et al.* (2010)[38]	Cohort	Greece	9·8	14 807	20–86	240	Pre- and postmenopausal	Premenopausal: not related to BC Postmenopausal: decrease in BC risk	FFQ MD score (0–9)
Buckland *et al.* (2012)[34]	Cohort	10 European countries	11	335 062	35–70	10 225	Pre- and postmenopausal	Premenopausal: not related to BC risk Postmenopausal: decrease in BC risk	FFQ MD score (0–16)
Cade *et al.* (2011)[56]	Cohort	UK	9	33 731	35–69	828	Pre- and postmenopausal	Premenopausal: decrease in BC risk Postmenopausal: not related	FFQ MD score (0–10)
Couto *et al.* (2013)[54]	Cohort	Sweden	16	44 840	30–49	1278	Pre- and postmenopausal	Not related to BC risk	FFQ MD score (0–9)
Castello *et al.* (2014)[58]	Case–control	Spain	–	2034	–	1017	Pre- and postmenopausal	Decrease in risk	FFQ MD score (0–9)
Murtaugh *et al.* (2008)[60]	Case–control	USA, Southwest	–	4119	25–79	757	Pre- and postmenopausal	Decrease in risk	FFQ
Castello *et al.* (2017)[59]	Multicase–control	Spain	–	1738	25–85	1181	Pre- and postmenopausal	Decrease in risk	FFQ
Turati *et al.* (2018)[61]	Case–control	Italy and Switzerland	–	3034	23–78	3034	Pre- and postmenopausal	Decrease in risk	FFQ MD score (0–9)

Breast cancer in premenopausalwomen and the Mediterranean diet: components

Fruit and vegetables

There is limited/suggestive evidence that intake of fruit and vegetables is inversely associated with BC risk in ER$^-$ BC[62,63]. Fruit and vegetable intake could represent a protective factor on BC due to high concentrations of bioactive components, such as carotenoids and polyphenols, substances with antioxidant and anti-inflammatory properties[64,65].

Carotenoids. Carotenoids are a family of pigmented compounds present in fruits and vegetables, which may protect

against DNA damage by neutralising reactive oxygen species (ROS)[66] and activating the antioxidant response element transcription system[67]. In fact, carotenoids act as scavengers of ROS and peroxyl radicals[68]. Carotenoids can neutralise radicals by different mechanisms: electron transfer, hydrogen abstraction and hydrogen addition. Due to the presence of conjugated double bonds, carotenoids can accept electrons from ROS, thus neutralising free radicals[69]. In addition to their antioxidant action, carotenoids also have anti-proliferative and pro-apoptotic actions; in an *in vitro* study, Gloria *et al.*[70] incubated human breast adenocarcinoma cell lines (MCF-7, MDA-MB-231 and MDA-MB-235) with lycopene and β-carotene (0·5–10 μM) for 48 and 96 h. After 96 h of treatment, lycopene significantly changed the cell viability in all cell lines. Lycopene treatment inhibited cell viability of MCF-7 and MDA-MB-235 cells by 30 and 20 %, respectively, while MDA-MB-231 cells were inhibited up to 75 %, showing the best response after 48 h, with a reduction of 30 %. After 48 h of treatment, β-carotene caused significant changes in cell viability of the three cell lines. The reduction was in the order of 40 % in the MCF-7 cell line, 30 % in MDA-MB-235 cells and 70 % in MDA-MB-231 cells. Furthermore, this study showed that lycopene increased the percentage of cells in the G0/G1 phase in the MCF-7 and MDA-MB-235 lines and also decreased the percentage of cells in the G2/M phase, thus highlighting the role of carotenoids as potential anti-tumour agents because of their ability to arrest cell proliferation and to induce apoptosis[71,72].

Polyphenols. Polyphenols present in fruit and vegetables have a wide range of biological functions[73]. Antioxidant activity is one of the key mechanisms that contributes to their protective effect against oxidative damage. Polyphenols are able to scavenge a broad spectrum of highly reactive species, such as ROS, oxidative N species, chlorine species, peroxynitrous acid (ONOOH) and hypochlorous acid (HClO); they also block the chain reactions of lipid peroxidation (chain breakers)[73]. Furthermore, polyphenols are involved in the reduction of the Fenton reaction, by chelation of Fe, thus protecting cells from oxidation from reactive hydroxyl radicals[74]. Moreover, the anti-cancer action of polyphenols might also be due to their anti-inflammatory activity, as they block the up-regulation of NF-κB, inhibit the phosphorylation and/or proteasomal degradation of IκB, inhibit the liberation of NF-κB dimers from the cytoplasm into the nucleus, and its interaction with target DNA sequences[75,76]. Another function of polyphenols is modulation of apoptosis. Chou *et al.*[77] incubated human breast adenocarcinoma cell lines MCF-7 with quercetin for 24 and 48 h and at various doses (10–175 μM), resulting in an approximate 90·25 % decrease in viable cells. Quercetin caused a remarkable increase in the number of S phase (14·56 to 61·35 %) and sub-G1 phase cells (0·1 to 8·32 %) in a dose- and time-dependent manner. Following incubation with quercetin for 48 h, MCF-7 cells showed apoptotic cell death, with a reduction in mitochondrial membrane potential, down-regulation of Bcl-2 protein and activation of the initiator caspases, caspase-8 and caspase-9, and the effector caspase, caspase-6, probably due to the binding of quercetin to the Fas/CD95 receptor[77]. Besides, some groups of flavonoids (the largest category of the polyphenols) act as a phyto-oestrogen and their anti-cancer action can be ascribed to their property of inhibiting aromatase activity[78]. In particular, there is a similarity between the A and C rings of flavonoids with the D and C rings of androstenedione, the substrate of aromatase[79]. In addition, flavones and isoflavones bind to oestrogen receptors (ER) and to the active sites of aromatase, thus influencing the promoter activity of aromatase[80,81].

Cohort studies and case–control studies. In a prospective cohort study, the association between fruit and vegetable intake and BC risk was evaluated in 47 289 Japanese women[82]. During an average of 10·2 years of follow-up, 452 new cases of BC were diagnosed. Cruciferous vegetable intake was associated with a statistically significant decrease in the risk of premenopausal BC (RR 4th *v.* 1st quartile 0·64; 95 % CI 0·38, 1·10; $P = 0·046$), with a marginal inverse association with ER^+/PR^+ tumours (RR per 100 g increment 0·64; 95 % CI 0·41, 1·00)[82]; in addition, a positive association was observed between both total intake of fruits and citrus fruits and BC risk in post- and premenopausal women[82]. Nevertheless, the bias in this study was the contemporary supplementary vitamin C intake and an extremely high intake of citrus fruit might lead to an increased risk of BC due to the extremely high dose of vitamin C[82]. Recently, Fervid *et al.*[83] evaluated the association between fruit and vegetable intake during adolescence and early adulthood and risk of BC in a cohort study including 90 476 women. The study participants completed a supplemental FFQ during high school (age range 13–18 years). During a follow-up of 22 years, a questionnaire was administered every 2 years, which allowed documentation of 3235 cases of invasive BC. A higher total fruit intake during adolescence was associated with a lower risk of premenopausal BC (HR 4th *v.* 1st quartile 0·75; 95 % CI 0·62, 0·90; $P = 0·01$). A high early adulthood intake of fruits and vegetables rich in α-carotene during early adulthood was also associated with a lower risk of premenopausal BC (HR 0·82; 95 % CI 0·70, 0·96) in those subjects in the highest quintile (median intake 0·5 servings/d) compared with those in the lowest quintile (median intake 0·03 servings/d)[83].

Whole grains

Evidence on the inverse association between intake of whole grains and BC risk still remains limited/inconclusive[84,85]. The protective action of whole grains is attributable to a high content of fibres and it has also been suggested that soluble and insoluble subtypes of dietary fibres may play a different role in the pathophysiological processes related to BC risk. Soluble fibres exert a protective role in the development of BC through various mechanisms, such as the insulin growth factor (IGF) pathway[86]. In particular, it has been reported that soluble fibres reduce the bioactivity of IGF-1, a major determinant in the pathogenesis and progression of a number of different cancers, notably by increasing IGF binding protein 3 (IGFBP3) concentration[87,88]. In addition, soluble fibres represent an effective controller of glucose and insulin homeostasis by slowing down glucose absorption, reducing insulin secretion and regulating the bioavailability of IGF. Instead, insoluble fibres, mainly found in seeds and whole grains, may help by down-regulating the

enterohepatic cycling of oestrogens with the consequent increase in their faecal excretion and decrease in their blood concentrations[89]. Moreover, fibres, especially soluble fibres, reduce inflammation as their fermentation in the colon produces SCFA that may exert an anti-inflammatory role[90–92] once penetrated into the bloodstream[93]. In fact, higher soluble fibre intake is associated with lower plasma levels of the pro-inflammatory cytokines IL-6[93,94].

Cohort studies and case–control studies. Several studies have examined the relationship between whole grain food intake and BC risk, but most analyses were focused on postmenopausal women[95–97]. Data regarding the association of fibres from whole grains and BC are, however, inconsistent, probably due to different effects from soluble *v.* insoluble fibres[98]. In a large cohort study, Cade *et al.*[99] evaluated the risk of developing BC and consumption of dietary fibres, in pre- and postmenopausal women. Data were collected from 35 792 women between 1995 and 1998 by using a postal questionnaire that included general questions on diet. During 240 959 subject-years of follow-up, 350 postmenopausal and 257 premenopausal developed invasive BC. In premenopausal, but not postmenopausal, women, a statistically significant inverse relationship between total fibre intake and risk of BC was found (RR 5th *v.* 1st quintile 0·48; 95 % CI 0·24, 0·96; $P = 0·01$). In particular, insoluble fibres from cereals were inversely associated with risk of BC ($P = 0·05$)[99]. Farvid *at al.*[100] evaluated individual grain-containing foods and whole and refined grain intake during adolescence, early adulthood, and premenopausal years in relation to BC risk in a population of 90 516 premenopausal women, within an age range of 25 to 42 years, from the Nurses' Health Study II. During the 22 years of follow-up 3235 women developed invasive BC. After adjustment for known BC risk factors, the authors concluded that intake in both adulthood and adolescence of whole-grain foods was associated with lower premenopausal BC risk (highest *v.* lowest quintile: RR 0·82; 95 % CI 0·70, 0·97; $P = 0·03$; RR 0·74; 95 % CI 0·56, 0·99; $P = 0·09$, respectively), but not with postmenopausal BC risk. It is interesting to note that these associations were mainly mediated by fibre intake in general, while no single food or type of grain appeared to account for these findings[100]. However, Ferrari *et al.*[101] in a cohort study, including 334 849 women, BC risk was inversely associated with total dietary fibre intake (HR 5th *v.* 1st quintile 0·95; 95 % CI 0·89, 1·01; $P = 0·03$) and fibre from vegetables (HR 5th *v.* 1st quintile 0·90; 95 % CI 0·84, 0·96; $P < 0·01$) but not with fibre from fruit, cereals or legumes. In line with these results, a case–control study conducted by Mourouti *et al.*[102] investigating the risk of developing BC in relation to consumption of whole grains in 250 cases and 250 controls evidenced that the consumption of whole grain for more than seven times per week was consistently associated with reduced risk of BC, especially in premenopausal women, whereas no significant association was observed in postmenopausal women. More specifically, whole grain consumption of more than seven times per week was associated with a 0·22-fold lesser risk of developing BC in premenopausal women (OR 0·22; 95 % CI 0·09, 0·54; $P = 0·001$)[102]. More recently, based on food frequency data from a population-based case–control study including 2135 BC cases in subjects of different ethnicity from the San Francisco Bay Area Breast Cancer Study, Sangaramoorthy *et al.*[103] also reported an association between dietary fibre intake and specific BC subtypes defined by ER and PR status. In this study, the authors confirmed that a high dietary intake of fibre-rich foods, such as beans and grains, may lower the risk of BC in both pre- and postmenopausal women. Of note, this study revealed a significant association between high dietary fibre intake and the aggressive BC subtype, such as ER^- and PR^- BC, for which few risk factors have been identified, thus supporting the importance of non-oestrogen-mediated mechanisms, for example, the IGF pathway[103].

Olive oil

Several studies have suggested that olive oil may be associated with a decreased BC risk[104,105], even if such a relationship has not been extensively studied in premenopausal women. The main active components of olive oil, the major source of energy in the MD, include monounsaturated lipids (especially oleic acid), phenolic constituents such as hydroxytyrosol, tyrosol (TY), glycoside-OL (oleuropein) and squalene[106]. Data from previous research studies attribute the anticancer effects of olive oil to its high content in oleic acid, the main MUFA in olive oil. In particular, oleic acid (18 : 1*n*-9) has been reported to suppress the overexpression of HER-2/ErbB-2, a well-characterised oncogene playing a key role in the aetiology, invasive progression and metastasis in several human cancers[107]. As mentioned above, olive oil is also an important reservoir of polyphenolic compounds, which are widely known for their anticancer properties. In particular, OL, 3,4-dihydroxyphenylethanol (HT) and TY[108,109] are potent antioxidants able to scavenge the superoxide anion, H_2O_2 and hypochlorous acid[110]. Phenolic compounds also possess anti-atherogenic, anti-thrombotic and anti-inflammatory properties[111,112]. Han *et al.*[113] demonstrated that HT and OL, at the dosage of 0·1 %, were able to decrease cell viability, inhibit cell proliferation and induce cell apoptosis in MCF-7 cells, with an increase in the number of cells in the G0/G1 phase. Moreover, olive oil polyphenols are able to interact with the NF-κB signalling pathway, which plays a pivotal role in the inflammatory response of the organism and represents an important target for preventing inflammation[114]. Briefly, the induction by any inflammatory stimulus of cyclo-oxygenase (COX)-2 gene, the master switch that activates the inflammatory response, is a prominent feature of all stages of BC[115–117]. COX-2 induction quickly results in the biosynthesis of prostaglandins of the E-series, particularly PGE_2, which in turn orchestrate the inflammatory response. Amplification of the COX-2 inflammatory cascade is triggered by recognition of proinflammatory stimuli by toll-like receptors on the cell membranes of exposed cells and activation of NF-κB, thereby initiating the production of cytokines, such as TNF-α, IL-1, IL-6 and IL-17, prostaglandins, chemokines and adhesion molecules[118]. In an *in vitro* study, Scoditti *et al.*[119] studied the effects of antioxidant polyphenols from virgin olive oil (OL and HT) on the angiogenic response in human vascular endothelial cells. The results of this study supported the potential protective role for dietary polyphenols in cancer as the authors reported a decreased angiogenesis via the inhibition of matrix metallopeptidase-9 (MM-9) and

COX-2, in association with a significant reduction in the stimulated intracellular ROS levels and in the activation of the redox-sensitive NF-κB[119].

Cohort studies and case–control studies. The largest case–control study providing data on BC risk and olive oil intake is an Italian investigation of 2569 cases and 2588 controls. In this study, La Vecchia *et al.*[120] examined the intake of olive oil and other dietary fats by FFQ. The OR for subsequent quintiles of olive oil intake compared with the lowest one were 1·05 (95 % CI 0·9, 1·3), 0·99 (95 % CI 0·8, 1·2), 0·93 (95 % CI 0·7, 1·2) and 0·87 (95 % CI 0·7, 1·1; $P=0·08$); however, no substantial differences were observed between pre- and postmenopausal women[120]. Subsequently, in a case–control study, Garcia-Segovia *et al.*[105] evaluated the risk of developing BC in relation to consumption of monounsaturated fat, in pre- and postmenopausal women. The study included a total of 755 women: 291 incident cases with confirmed BC and 464 controls randomly selected from the Canary Island Nutrition Survey (ENCA). Data regarding the usual dietary patterns were collected by using FFQ, and the results supported the protective role of olive oil consumption on BC in Canary Islands women (OR 5th *v.* 1st quintile 0·27; 95 % CI 0·17, 0·42; $P=0·07$), but the authors did not investigate the differences related to menopausal status[105]. Furthermore, an increased risk of BC was shown to be associated with higher mammographic density[121–123], and, currently, it is proposed as an intermediate phenotype for identifying women with a higher risk of BC[124,125]. In a cross-sectional study, García-Arenzana *et al.*[126] assessed the association between mammographic density and diet among 3548 pre- and postmenopausal women extracted from seven BC screening programmes in Spain. The results showed that an increase in olive oil consumption of two tablespoons per d (22 g) was associated with a lower mammographic density (OR 0·72; 95 % CI 0·56, 0·93; $P=0·008$), with no differences concerning menopausal status[126].

Fish

Some studies indicate the existence of an inverse association between high intake of fish food and BC risk[127,128], but again most analyses were focused on postmenopausal women[129]. The protective effect of the consumption of seafood is mainly due to the high content of *n*-3 PUFA. α-Linolenic acid (18 : 3*n*-3) is the precursor of the *n*-3 PUFA family, which can be further elongated and desaturated to two important long-chain *n*-3 PUFA: EPA (20 : 5*n*-3) and DHA (22 : 6*n*-3)[130]. These classes of PUFA inhibit mammary carcinogenesis at all stages of cancer: initiation[131], promotion[132] and progression[133], in both *in vitro* and animal studies. One of the key cellular functions of PUFA in reducing tumour development is the inhibition of the synthesis of inflammatory eicosanoids derived from arachidonic acid (AA)[134]. In fact, higher intakes of α-linolenic acid reduce the synthesis of AA from linoleic acid (18 : 2*n*-6) and, thus, less AA is available for the synthesis of inflammatory eicosanoids[135,136]. Moreover, EPA also has other complementary actions on COX-2, as it displaces AA as an enzymic substrate of COX-2 and decreases expression of COX-2[137], thus limiting the rate of PGE_2 synthesis[138,139].

Cohort studies and case–control studies. In a case–control study, Goodstine *et al.*[140] investigated the association between the intake of *n*-3 and other fatty acids and the *n*-3:*n*-6 PUFA ratio and BC risk. In premenopausal women, the consumption of the lowest ratio of *n*-6 to *n*-3 was associated with a non-statistically significant 41 % reduction of BC risk (OR 0·59, 95 % CI 0·29, 1·19; $P=0·09$)[140]. In a subsequently case–control study, Kim *et al.*[141] confirmed these data. The authors investigated the association between fish intake and the incidence of BC in Korean women in 362 patients with incident BC, within an age range of 25 to 77 years. Premenopausal women revealed a significant reduction in BC risk for the highest intake quartiles of *n*-3 fatty acids (OR 4th *v.* 1st quartile 0·46; 95 % CI 0·22, 0·96), compared with the lowest quartile taken as reference group[141]. In the Japan cohort study, a significant decrease in the risk of BC was detected in women with the highest dietary intake of fish fat and long-chain *n*-3 PUFA. In this study, Wakai *et al.*[142] examined 26 291 women within an age range of 40 to 79 years, who completed a questionnaire on dietary and other factors. During the period of 7·6 years of follow-up 129 incident cases of BC were documented. A significant decrease in risk was detected for the highest quartile of intake compared with the lowest quartile for fish fat and long-chain *n*-3 fatty acids intake; the RR were 0·56 (95 % CI 0·33, 0·94; $P=0·034$) and 0·50 (95 % CI 0·30, 0·85; $P=0·042$), respectively. For premenopausal women at baseline, the RR for the higher quartiles of long-chain *n*-3 fatty acids were lesser than 1, but far from significant levels[142]. Similar results were found in another cohort study, where Murff *et al.*[143] investigated the association of dietary PUFA and the ratio of *n*-6 PUFA:marine-derived *n*-3 PUFA with BC risk in the Shanghai Women's Health Study. The authors determined dietary fatty acid and fish intake by using FFQ. This study showed no association between *n*-3 PUFA intake and BC risk, while a low *n*-3 PUFA intake in women who had the highest *n*-6 PUFA was positively correlated with an elevated BC risk. These studies indicated the necessity of higher *n*-3 PUFA intakes, *n*-6 intakes being generally adequate in all populations, and thus emphasising the potential value of *n*-3 PUFA as effective agents against BC. No significant differences in individual PUFA effect were observed between pre- and postmenopausal women[143].

Moderate red wine drinking

Alcohol consumption, including wine, has been consistently associated not only with an increased risk of BC[144–146], but also with breast density in both pre- and postmenopausal women[147–149]. The mammary epithelium expresses class I alcohol dehydrogenase and the tissue may be susceptible to an intermediate metabolite of ethanol oxidation (acetaldehyde), responsible for DNA damage and activation of the Fantoni anaemia-BC susceptibility (FA-BRCA)[144,150]. Marietta *et al.*[151], in fact, recently showed that the exposure of human cells to acetaldehyde resulted in activation of the FA-BRCA network, as indicated by increased FANCD2 mono-ubiquitination and phosphorylation of BRCA1. Consistent with a DNA damage response, acetaldehyde generates several different types of DNA adducts that can block DNA replication in humans[152]. However, considering the healthy effects of red wine in the prevention and treatment

of several chronic diseases[153], it is questionable whether also a moderate intake red wine could raise the risk of BC (WCRF)[23]. Indeed, red wine is rich in phenolic compounds, such as resveratrol, which exert anti-inflammatory and antioxidant effects and could act as protective factors in BC development[154]. Resveratol is a natural polyphenol present in fruit with red skins, including grapes, and it is therefore also present in high concentration in wine, especially red wine. Resveratrol is also involved in the activation of the protein SIRT1, an enzyme that is a member of the sirtuin family of proteins, which is capable of regulating the activity of certain transcription genes that are involved in the regulation of appetite[155]. Thus, SIRT1 affects the regulation of energy balance, which in turn can aid in the prevention of diet-dependent obesity and related metabolic disorders[155]. Also, resveratrol plays a key role in the prevention of cancer by blocking the process of initiation, promotion and progression[155]. As a phyto-oestrogen, it regulates the expression of numerous genes associated with the development of BC, including a tumour suppressor BRCA1 gene[156]. Phytochemicals could also account for different potential mechanistic pathways as red wine is also endowed with anti-oestrogenic activity[157] and may serve as a nutritional aromatase inhibitor[153]. Nonetheless, the protective role of moderate quantities of red wine at meals for reducing BC risks remains questionable.

Cohort studies and case–control studies. In a cross-over study conducted in healthy premenopausal women, Shufelt *et al.*[153] compared red wine and white wine consumption and showed that red wine was associated with significantly lower levels of total and free testosterone and sex hormone-binding globulin, as well as a significantly higher levels of luteinising hormone, although without significant differences in oestradiol levels. In a case–control study in Southern France, Bessaoud & Daures[158] evaluated the effects of drinking patterns of alcoholic beverages on BC risk, focusing on wine consumption in particular. The study reported a lower risk of BC among women consuming 10–12 g/d of wine (OR 0·51; 95 % CI 0·30, 0·97) when compared with non-wine drinkers, but they did not evaluate red and white wine separately, or the difference of risk between pre- and postmenopausal women[158]. Nevertheless, in a cohort study, Fagherazzi *et al.*[159] evaluated the interaction between alcohol intake and BC risk in pre- and postmenopausal women. This study showed a positive trend in BC risk with increasing alcohol intake in the overall population ($P_{trend} = 0·0003$), and women who consumed more than two standard drinks per d had a significant 19 % increase in risk (HR 1·19; 95 % CI 1·04, 1·36), but, this association was limited to postmenopausal women ($P_{trend} < 0·0001$ and HR 1·24; 95 % CI 1·07, 1·44)[159].

Red meat

It is known that processed or cooked red meat is a source of carcinogens, due to the generation of heterocyclic amines, *N*-nitroso compounds and polycyclic aromatic hydrocarbons generated during high-temperature cooking, which are responsible for an increase in BC risk in humans, as demonstrated in numerous *in vitro* and *in vivo* test systems[160]. In particular, heterocyclic amines display oestrogenic activity and breast tissue-specific carcinogenic activity has been reported[161]. In addition, several studies have suggested that induction of lipid peroxidation mediated by free radicals of the fats found in red and processed meats could be another mechanism by which processed red meat may promote carcinogenesis[162,163].

Cohort studies and case–control studies. Several studies have investigated the relationship between intake of red meat and risk of BC in premenopausal women[164,165]. In a prospective study, Linos *et al.*[164] investigated red meat intake during adolescence and BC incidence in a group of 39 268 premenopausal women, within an age range of 25 to 43 years. During a 7-year follow-up, 455 women developed invasive BC[164]. Women who consumed the greatest quantity of red meat during high school had a 30 to 40 % higher risk of BC as compared with women with the lowest intake of red meat (RR 5th *v.* 1st quintile 1·34; 95 % CI 0·94, 1·89; $P = 0·05$). A significant linear association was observed with every additional 100 g of red meat consumed per d (RR 1·20; 95 % CI 1·00, 1·43; $P = 0·05$). Furthermore, this association was more pronounced in ER-positive subjects (RR 1·36; 95 % CI 1·08, 1·70; $P = 0·008$) and was not significant in ER-negative women (RR 0·99; 95 % CI 0·61, 1·61; $P = 0·97$)[164]. Later, these results were confirmed by Farvid *et al.*[166] in a population study. The authors investigated the consumption of red meat during adolescence as related to BC risk in the Nurses' Health Study II cohort[166]. The cohort consisted of a total of 116 430 females that completed an FFQ about their diet while in high school. During a 13-year follow-up, 1132 new cases of BC were documented. In this study a greater consumption of total red meat was significantly associated with a higher risk of premenopausal BC (RR 5th *v.* 1st quintile 1·42; 95 % CI 1·05, 1·94; $P = 0·007$), contrary to what was observed in postmenopausal BC[166]. In line with these results, in a very recent prospective study, Diallo *et al.*[167] evaluated the prospective associations between red and processed meat intakes and overall, breast and prostate cancer risk. The study included 61 476 men and women with an age of at least 35 years who completed three 24 h dietary records during the first years of follow-up. During the follow-up 1609 incident cancer cases were diagnosed, among which 544 BC. Red meat intake was associated with increased overall cancer risk (HR 5th *v.* 1st quintile 1·31; 95 % CI 1·10, 1·55; $P = 0·01$) and increased BC risk (HR 5th *v.* 1st quintile 1·83; 95 % CI 1·33, 2·51; $P = 0·002$). This association between red meat intake and increased BC risk was observed in both premenopausal women (HR 5th *v.* 1st quintile 2·04; 95 % CI 1·03, 4·06) and postmenopausal women (HR 5th *v.* 1st quintile 1·79; 95 % CI 1·26, 2·55)[167].

Nuts

Nuts are a rich source of nutrients, such as PUFA, proteins, fibres, vitamins, minerals, antioxidants and phytochemicals, including phenolic compounds and phytosterols[168]. The multiple mechanisms of the anti-tumoural effect of these components are related to their antioxidant activity, regulation of cell differentiation and proliferation, reduction of tumour initiation or promotion, repair of DNA damage, anti-inflammatory effects,

immunoregulatory activity, induction or inhibition of metabolic enzymes and hormonal mechanisms[169,170].

Cohort studies and case–control studies. The evidence of nut intake and BC risk is only limited and focused on postmenopausal women[171]. Extrapolating data from the above-mentioned cohort study by Farvid *et al.*[166] on adolescent meat intake and BC risk, the authors found that there was no significant association between adolescent intake of nuts and premenopausal BC. In a case–control study, Liu *et al.*[172] investigated the associations of dietary fibres, vegetable proteins, vegetable fat and nuts consumed during adolescence with adult BC risk (OR 5th *v.* 1st quintile 0·76; 95 % CI 0·61, 0·95 for > serving/d *v.* < 1 serving/month intake; $P = 0·04$). The study included 2865 cases and 3299 controls who furnished information on their diet habits during adolescence through an FFQ[172]. The results showed that nut intake during adolescence was inversely associated with BC risk. These results were comparable in pre- and postmenopausal BC[172].

Legumes

Some studies indicate the existence of an inverse association between high intake of legumes and BC risk. However, considering the limited number of studies it was not possible to conduct analyses according to menopausal status[34,173]. As reported above, the protective effect of legumes is attributable to their high content of fibres, in particular soluble fibres. In addition, lignans and phytic acid from legumes have shown antioxidative and anticarcinogenic potential[174].

Cohort studies and case–control studies. In a case–control study, Sangaramoorthy *et al.*[103] evaluated the risk of developing BC and consumption of dietary bean fibre in pre- and postmenopausal women. Data were collected from 17 581 women aged 35–79 years and newly diagnosed with a first primary invasive BC by using a FFQ that included general questions on diet and on fibre intake. The authors reported that there was a 20 % reduction in BC risk with high intake (high *v.* low quartile) of bean fibre ($P_{trend} = 0·01$), total beans ($P_{trend} = 0·03$) or total grains ($P_{trend} = 0·05$). Inverse associations were strongest for ER^-/PR^- BC, with a risk reduction associated with high intake ranging from 28 to 36 %, without differences in pre- and postmenopausal women[103]. In the Nurses' Health Study, Adebamowo *et al.*[175] evaluated the risk of developing BC and consumption of flavonol-rich foods intake in premenopausal women, aged between 26 and 46 years. Among the major food sources of flavonols, a significant inverse association with the intake of beans or lentils has been reported. The multivariate RR, comparing the highest category (or more times per week) of cumulative average beans or lentils intake with the lowest category (less than once per month), was 0·76 (95 % CI 0·57, 1·00; *P* for test of trend = 0·03)[175].

Conclusions

Diet is a modifiable factor risk for BC and several studies have reported that low intake of vegetables and fruit and high consumption of red and processed meat increase the risk of developing BC. Epidemiological studies indicate an increase in cases of BC in a younger age at diagnosis. Premenopausal BC is also highly associated with a significantly increased risk of cancer recurrence and higher mortality rate. Despite there being a growing interest in preventive strategies to tackle the increasing rate of premenopausal BC incidence, the role of the MD and its main components in premenopausal women has not yet been sufficiently investigated. Prospective cohort and case–control studies suggested that high adherence to a diet based on the MD pattern, rich in *n*-3 PUFA, fruits, vegetables, fibres, in association with a reduced intake of red meat and a moderate red wine consumption, gives a significant protection against incidence of BC in postmenopausal women. The protective effects of the MD might be due to several mechanisms, involving the regulation of cell proliferation, induction of apoptosis, and antioxidant action. Although limited by several methodological biases that might potentially affect or influence the interpretation of the findings, including sampling methodology and characteristics of the population included, the studies included in the present review indicate that currently there is no sufficient scientific evidence to support that adherence to the MD pattern is associated with a decrease in BC risk or with specific BC characteristics in premenopausal women. This evidence is in striking contrast to the well-known anti-cancer effects of the MD. Nevertheless, focusing separately on the effects of the main components of the MD, there is an overall agreement that in premenopausal women a high total fruit intake, as well as the intake of insoluble fibres, the regular consumption of whole grains or the intake of nuts, especially during adolescence, are consistently associated with a reduced risk of BC, whereas a high consumption of red meat during adolescence is associated with a high risk of BC. On the contrary, an increase in olive oil and PUFA-rich food consumption, such as fish, and moderate red wine consumption are associated with a lower risk of BC, but without differences concerning menopausal status. On these bases, the clinical and experimental evidence reported in the present review underlines that an accurate nutritional counselling based on healthy dietary choices and lifestyle modifications should be an integral part of the management of premenopausal women with BC and might be of strategic relevance in terms of the prevention of BC. These recommendations should become part of a normal lifestyle during early childhood, when the mammary glands may be particularly vulnerable to breast carcinogenesis due to rapid proliferation of cells and lack of terminal differentiation. However, long-term studies are needed to further confirm the beneficial effect of the MD and of its components in the prevention of BC in premenopausal women.

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