



Revisión

Mediterranean diet adherence and prostate cancer risk

Olga López-Guarnido¹, Maria Jesús Álvarez-Cubero^{1,2,5}, María Saiz^{1,2,5}, David Lozano¹, Lourdes Rodrigo¹, Manrique Pascual³, Jose Manuel Cozar³ and Ana Rivas⁴

¹Legal Medicine and Toxicology Department, University of Granada, Granada, Spain. ²Center GENYO (Pfizer-University of Granada-Andalusian Government Center for Genomics and Oncological Research), Granada, Spain. ³Service of Urology, University Hospital Virgen de las Nieves, Granada, Spain. ⁴Nutrition and Food Science Department, University of Granada, Granada, Spain.

Abstract

Background: Countries following the traditional Mediterranean Diet, particularly Southern European countries, have lower prostate cancer incidence and mortality compared to other European regions. The beneficial effect has been attributed to a specific eating pattern.

Objective: The purpose of this review is to examine the evidence to date on the effects of adherence to a Mediterranean Diet on prostate cancer risk; and to identify which elements of the Mediterranean diet are likely to protect against prostate cancer.

Methods: The search for articles came from extensive research in the following databases: PubMed, Scopus and Web of Science. We used the search terms “Mediterranean diet”, “adherence”, “fruit and vegetable”, “olive oil”, “fish”, “legume”, “cereal”, “alcohol”, “milk”, “dairy product”, “prostate cancer”, and combinations, such as “Mediterranean diet and prostate cancer” or “Olive oil and prostate cancer”.

Results: There is strong evidence supporting associations between foods that are typical of a Mediterranean eating pattern and reduced prostate cancer risk. However, there are few studies that have assessed the effect of the Mediterranean diet on cancer prostate incidence. Recent data do not support associations to adherence to a Mediterranean Diet and risk of prostate cancer or disease progression. However, Mediterranean eating pattern after diagnosis of nonmetastatic cancer was associated with lower overall mortality.

Conclusion: Further large-scale studies are required to clarify the effect of Mediterranean diet on prostate health, in order to establish the role of this diet in the prevention of prostate cancer.

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Key words: Mediterranean diet. Nutrition. Prostate cancer.

Correspondence: Ana Rivas Velasco.
Dpto. Nutrición y Bromatología.
Facultad de Farmacia, Campus de Cartuja.
Universidad de Granada, 18071 Granada.
E-mail: amrivas@ugr.es

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⁵These authors contributed equally to this work.

ADHERENCIA A LA DIETA MEDITERRÁNEA Y CÁNCER DE PRÓSTATA

Resumen

Introducción: Los países del sur de Europa, tienen una menor incidencia y mortalidad por cáncer de próstata en comparación con otras regiones europeas. Este efecto beneficioso se ha atribuido a un patrón de alimentación específica.

Objetivo: El objetivo de esta revisión es examinar la evidencia sobre los efectos de la adhesión a la dieta mediterránea en el riesgo de cáncer de próstata; e identificar que componentes de la dieta mediterránea protegen contra el cáncer de próstata.

Métodos: Se realizó una búsqueda en la literatura científica utilizando las siguientes base de datos: PubMed, Scopus and Web of Science. Utilizamos los términos de búsqueda “dieta mediterránea”, “adhesión”, “frutas y verduras”, “aceite de oliva”, “pescado” “legumbres”, “cereal” “alcohol” “leche”, “producto lácteo”, “cáncer de próstata”, y combinaciones, tales como “dieta mediterránea y cáncer de próstata” o “aceite de oliva y cáncer de próstata”.

Resultados: Existe una fuerte evidencia que soporta una asociación entre alimentos que son típicos de un patrón de alimentación mediterránea y un menor riesgo de cáncer de próstata. Sin embargo, son pocos los estudios que han evaluado el efecto de la dieta mediterránea sobre la incidencia del cáncer de próstata. Los datos recientes no apoyan una asociación entre el seguimiento de este tipo de dieta y el riesgo de cáncer de próstata o su progresión. Sin embargo, un patrón de alimentación mediterránea después del diagnóstico de cáncer no metastásico se ha asociado con una disminución de la mortalidad global.

Conclusión: Se requieren más estudios a gran escala para aclarar el efecto de la dieta mediterránea sobre la salud prostática, con el fin de establecer su papel en la prevención de cáncer de próstata.

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Palabras Clave: Dieta Mediterránea. Cáncer de Próstata. Nutrición.

Introduction

Prostate cancer (PCa) is the second most common cancer in men worldwide, after lung cancer, but still little is known about the etiology of this disease¹. Epidemiological studies have suggested that environmental exposure, including diet and nutrition, may play a role in its etiology because of the wide international variation in its incidence². The dramatic increase in its occurrence among migrants from low-risk to high-risk countries also points to this hypothesis³. The World Cancer Research Fund has identified selenium, lycopene, and calcium as probable modifiers of PCa risk^{4,5}. In addition, animal model studies implicate dietary carcinogens, such as the heterocyclic amines from over-cooked meats and sex steroid hormones, particularly estrogens, as candidate etiologies for PCa⁶. With dietary carcinogens and estrogens driving pro-carcinogenic inflammation in the developed world, it is tempting to speculate that dietary components associated with decreased PCa risk, such as intake of fruits and vegetables, especially tomatoes and crucifers, might act to attenuate the ravages of the chronic or recurrent inflammatory processes⁶.

To date, the most consistently followed approach to examine the potential relation between dietary factors and PCa was based on particular nutrients such as lycopene and selenium. However, results from studies on individual nutrients are largely inconsistent. This might be partly due to limitations in single nutrient investigations owing to that we do not eat isolated nutrients but meals consisting of a variety of foods with complex combinations of nutrients and bioactive components. The traditional analysis considering the effect of a few isolated nutrients on prostate health misses much key information regarding complex or cumulative correlations and interactions between these compounds contained in food. For this reason, there is an increasing interest in the study of dietary patterns that could answer some questions and promote the development of appropriate recommendations for overall dietary habits⁷.

Prostate cancer has emerged as the most frequent cancer amongst men in Europe, with incidence increasing rapidly over the past two decades. Countries following the traditional Mediterranean Diet (MeDi), particularly Southern European countries, have lower PCa incidence and mortality compared to other European regions⁸. The beneficial effect has been attributed to a specific eating pattern. The Mediterranean diet's key characteristics are high intake of vegetables, legumes, fruits and cereals; moderate to high intake of fish; low intake of saturated lipids and high intake of unsaturated lipids, particularly olive oil; low to moderate intake of dairy products, low intake of meat; and modest intake of ethanol, mostly in the form of wine.⁹ The MeDi was introduced to the scientific community by the classic Seven Countries study. Since then, data on the association between this diet and lower risk of can-

cer at various sites have been accumulating^{10,11}. However, a limited number of cross-sectional studies have examined the relationship between MeDi adherence and PCa, and they have reported conflicting results. Therefore, the purpose of this review is to examine the evidence to date on the effects of adherence to a Mediterranean diet on prostate cancer risk and to identify which elements of the Mediterranean diet are likely to protect against prostate cancer.

Methods

The search for articles came from extensive research in the following databases: PubMed, Scopus and Web of Science. We used the search terms "Mediterranean diet", "adherence", "fruit and vegetable", "olive oil", "fish", "legume", "cereal", "alcohol", "milk", "dairy product", "lycopene", "vitamin E", "vitamin C", "resveratrol", "prostate cancer", and combinations, such as "Mediterranean diet and prostate cancer" or "Olive oil and prostate cancer". The titles and abstracts of the located documents were initially reviewed and the reference lists of selected papers were searched to identify additional articles. We narrowed the search to studies published in English.

Results and discussion

Adherence to Mediterranean diet and prostate health

The MeDi is characterized by a high intake of olive oil, plant products, fish and seafood; a low intake of dairies, meat and meat products; and a moderate ethanol intake⁹. These food items contain a complex array of naturally occurring bioactive molecules with antioxidant, anti-inflammatory and alkalinising properties that may protect against PCa. In order to analyze the role of Mediterranean eating habits on PCa risk, dietary pattern analyses should be considered. These studies examine the association between overall diet and disease risk, taking into account the fact that foods are eaten in combination¹². The ability of a diet quality index score to predict PCa risk depends on how well the index measures dietary risk factors for PCa as these indices have been associated with other chronic disease outcomes¹³⁻¹⁴.

Previous studies on dietary patterns and risk of PCa have used different methodological approaches and reported inconsistent findings¹⁴. A small, clinic based case-control study conducted in Canada reported that men in the highest tertile for the processed pattern, which key characteristics are consumption of red meats, organ meats, processed meats, refined grains, vegetable oils, and soft drinks, had an adjusted odds ratio (OR) of 2.75 [95% confidence interval (CI): 1.40-5.39, $p=0.0035$]. On the other hand, the Western diet, characterized by high intake of energy, red

meats and fat, and low intake of fiber, has been associated with an increased risk for advanced PCa according to separate Australian¹⁵ and Uruguayan studies¹⁶; however, in 3 prospective studies in US men, investigators found no significant association between any identified dietary patterns and the risk of PCa. incidence¹⁷⁻¹⁹. Recently, Bosire et al. incidence¹⁴ investigated the relationship between index-based dietary patterns and the risk of PCa in a cohort of 293,464 US men. Among men who reported a history of prostate-specific antigen testing, high Healthy Eating Index-2005 (HEI-2005), and Alternate Healthy Eating Index-2010 (AHEI-2010) scores were associated with lower risk of total PCa (for the highest quintile compared with the lowest), [hazard ratio (HR) = 0.92, 95% CI: 0.86-0.98, $p = 0.01$; and HR = 0.93, 95% CI: 0.88, 0.99, $p = 0.05$, respectively]. No significant association was observed between any of the indices and advanced or fatal PCa. Eating habits based on cornbread, grits, sweet potatoes, okra, beans, and rice—that is, similar to those of the MeDi—were proven by the National Health and Nutrition Examination Survey Epidemiological Follow-up study to be significantly associated with PCa risk¹⁹. Both black and nonblack men in the highest tertile for this dietary pattern had a reduced risk of PCa (OR=0.6, 95% CI: 0.4-1.10, $p = 0.008$).

There are a few studies that have assessed the effect of the MeDi on cancer prostate incidence. Besides these, the impact of MeDi adherence on prostate health remains unclear. Table I summarizes the characteristics of these studies: where the work was conducted, the number of participants in each study, the methods used to evaluate MeDi adherence, and the main results. A comprehensive review of studies on cancer and the Mediterranean dietary pattern in the Mediterranean region incidence²⁰ concluded that adherence to principles of the MeDi may significantly reduce PCa incidence. Trichopoulou and coworkers used effect estimates from studies of dietary intake and cancer in the Mediterranean region, incidence rates of PCa, and food consumption patterns to calculate the fraction of PCa incidence that could be avoided by adherence to the principles of the MeDi. They estimated that approximately 10% of PCa cases in the United States could be prevented by adherence to the traditional healthy MeDi. Kenfield et al.²¹ described that adherence to a MeDi evaluated through a Mediterranean Diet Score (MDS) was not associated with risk of advanced PCa or disease progression in a prospective study following 47,867 US men in the Health Professionals Follow-up Study. However, greater adherence to the MeDi after diagnosis of non-metastatic cancer was associated with lower overall mortality. Bosire et al.¹⁴ examined the relationship between diet quality and the risk of PCa in the National Institutes of Health (NIH)-AARP Diet and Health Study cohort (293,464 US men) using the alternate Mediterranean diet score (aMED). There was no association between total PCa and the aMED score

(HR=0.97, 95% CI: 0.91, 1.03, $p = 0.09$). In addition, it was found little support for an association between the MeDi and PCa in a Northern European case-control study²². The authors defined five MDS variants with different components using either study-specific intakes or intakes in a Greek reference population as cut-off values between low and high intake of each component. No statistically significant association was found between adherence to the MeDi based on any of the MDS variants and PCa risk (OR range: 0.96–1.19 for total PCa, comparing high with low adherence). Recently, Ax et al.⁴ studied the relationship between adherence to a modified Mediterranean Diet Score (mMDS) and PCa risk in the Uppsala Longitudinal Cohort Study of Adult Men. No associations were found between Mediterranean dietary patterns and PCa in the whole study population (HR = 1.0, 95% CI: 0.75-1.34; $p = 0.91$).

Components of the Mediterranean diet and prostate cancer

There is evidence that specific components of MeDi are involved in prostate carcinogenesis prevention. In this context, the principal studies that demonstrate this association are described below.

Olive oil as the principal source of fat

Olive oil is the major common characteristic of diet in Mediterranean populations, where it accounts for one to two-thirds of total vegetable fat intake, and is therefore a relevant source not only of unsaturated fats, but of several other dietary components and micronutrients, as well.²³ Various studies have consistently revealed that total fat intake and particularly saturated fat intake were significantly associated with an increased risk for advanced PCa.^{16,24} However, dietary intake of monounsaturated and polyunsaturated fat was generally not associated with advanced PCa risk^{16,25,26}.

A Greek study provided limited data on added lipids -including olive oil- and PCa risk. The authors concluded that among added lipids, seed oils were significantly associated, and butter and margarine were non-significantly positively associated with PCa risk, whereas olive oil was unrelated to this risk²⁷. An Australian case-control study compared subjects consuming <0.25 and ≥ 0.25 l/month to non users of olive oil, and reported no significant association between olive oil consumption and PCa risk (both ORs=0.8)²⁸. A population-based case-control study was conducted in Auckland, New Zealand, involving 317 PCa cases and 480 controls²⁹. A food-frequency questionnaire was used to collect data concerning consumption of monounsaturated fatty acids (MUFA)-rich vegetable oils (including olive oil, canola or peanut

Table I
Description of the studies that have assessed the effect of the Mediterranean diet on prostate cancer

Reference	Country	Subjects	Type of study	Method used to evaluate MeDi adherence	Results	Conclusions
Kenfiel et al. ²¹	USA	N= 42867 Aged 40-75 yr	The Health Professionals Follow-up Study Prospective cohort	MeDi Score Alternative MeDi Score	The MeDi was not associated with risk of advanced (HR: 0.95; 95% CI: 0.81-1.11; p=0.56) or lethal PCa (HR: 0.95; 95% CI: 0.79-1.13; p=0.65). In the case-only analysis, there was no association between the MeDi after diagnosis and risk of lethal (HR: 0.98; 95% CI: 0.75-1.29; p=0.76) or fatal PCa (HR: 1.01; 95% CI: 0.75-1.38; p=0.95). There was a 22% lower risk of overall mortality (HR: 0.78; 95% CI: 0.67-0.90; p=0.0007) among men with greater adherence to the MeDi after PCa diagnosis	A higher MeDi score was not associated with risk of advanced PCa or disease progression. Greater adherence to the MeDi after diagnosis of nonmetastatic PCa was associated with lower overall mortality
Bosire et al. ¹⁴	USA	N= 293464 Aged 50-71 yr	the National Institutes of Health (NIH)-AARP Diet and Health Study Prospective cohort	Alternative MeDi Score	There was no association between total PCa. and the alternative MeDi score (HR = 0.97, 95% CI: 0.91-1.03; p = 0.09)	No significant association was observed between alternative MeDi score and total PCa or advanced or fatal PCa, regardless of prostate-specific antigen testing status
Möller et al. ²²	Sweden	N=1482 cases, 1108 controls	Aged 35–79 yr	Cancer of the Prostate in Sweden (CAPS) study.	Case-control MeDi Score	Five MeDi Score variants. No statistically significant association was found between adherence to the MeDi based on any of the MDS variants and PCa risk (OR range: 0.96–1.19 for total PCa, comparing high with low adherence)
Ax et al ⁴	Sweden	N=1044 Mean age 71±1 yr	Uppsala Longitudinal Study of Adult Men Prospective cohort	A Modified MeDi Score	There were no associations between modified MeDi score and PCa in the whole study population (HR = 1.0, 95% CI: 0.75-1.34; p = 0.91)	No association was found between a Mediterranean-like diet and PCa risk

MeDi: Mediterranean diet; PCa: Prostate cancer; HR: Hazard ratio; OR: Odds ratio; CI: Confidence interval.

oil) and other dietary variables. Increasing levels of MUFA-rich vegetable oil intake were associated with a progressive reduction in PCa risk [Relative risk (RR)= 0.5; 95% CI: 0.3-0.9; > 5.5 ml per day vs. nonconsumption, $p= 0.005$]. However, PCa risk was not associated with intake of total MUFA or its major

animal food sources. The authors conclude that their finding may be attributable to a protective dietary pattern associated with their consumption involving a high intake of plant-derived foods and fish oils, to a specific protective effect of these oils or to a combination of these factors²⁹.

Regular consumption of fish

Fish consumption is a characteristic component of the traditional MeDi. Cross-national studies showed inverse associations between per capita consumption of fish and the incidence of and mortality rates from PCa^{30,31}. Pre-clinical studies utilizing xenografts and genetically engineered mouse models demonstrated that reducing dietary fat from corn oil and increasing fish oil intake delays the development and progression of PCa^{32,33}. Moreover, intake of fish and marine-derived ω -3 fatty acids has been shown to be associated with decreased PCa mortality³⁴. It should be noted that ω -3 fatty acids have been shown consistently to inhibit the proliferation of PCa cell lines in vitro and to reduce the risk and progression of these tumors in animal experiments³⁵. Various biological mechanisms have been proposed to explain these findings, e.g., a reduction in circulating testosterone concentrations³⁶.

A meta-analysis of fish intake and PCa concluded that there was an association between fish consumption and a significant 63% reduction in PCa-specific mortality [4 cohort studies (n = 49,661), RR: 0.37; 95% CI: 0.18-0.74]³⁷. Recently, Bosire and coworkers¹⁴ showed that in individual component analyses, the fish component of Alternate Mediterranean Diet Score and ω -3 fatty acids component of Alternate Healthy Eating Index were inversely associated with fatal PCa (HR = 0.79, 95% CI: 0.65-0.96, and HR = 0.94, 95% CI: 0.90-0.98, respectively).

High consumption of fruit and vegetables

Fruits and vegetables are an important element of the MeDi and are rich in fiber, micronutrients, and phytochemicals which may have anti-carcinogenic actions². A few case-control studies have reported an overall inverse association between intake of fruits and vegetables and the risk for advanced PCa. Kolonel et al.³⁸ reported that yellow-green vegetables, cruciferous vegetables and carrots were associated with a 33% reduced risk for advanced PCa. Hardin et al.³⁹ investigated the associations between vegetable, fruit, and grains and more aggressive PCa in a case-control study of 982 men. Comparing the highest to lowest quartiles of intake, the authors found that increasing intakes of leafy vegetables were inversely associated with risk of aggressive PCa (OR = 0.66, 95% CI: 0.46-0.96, $p = 0.02$). The results from cohort studies examining the association between intake of fruits and vegetables and the risk of advanced PCa were largely inconsistent²⁴. Takachi et al.⁴⁰ did not find any association between fruit intake and the risk for advanced PCa. A recent metaanalysis that included 16 cohort studies² showed that the combined adjusted relative risk comparing highest with lowest categories showed that there was no association between vegetable and

fruit consumption and PCa incidence. The pooled RR was 0.97 (95% CI: 0.93-1.01) for vegetables and 1.02 (95% CI: 0.98-1.07) for fruit. The authors concluded that the intakes of certain types of fruit and vegetables may be more important than others in reducing the risk of PCa, owing to the different compounds found in each.

High consumption of legumes and cereals

Cereals and legumes are the main energy sources in the MeDi. It should be noted that high consumption of these foods, increases the intake of vegetable fiber, which is involved in the neoplastic risk by reducing the glycemic load, improving insulin sensitivity and decreasing the concentration of IGF-1⁴¹. Higher intake of legumes and cereals has been associated with a decreased risk of several cancers⁴². In addition, Deschaux et al.⁴³ showed that PCa risk was inversely associated with legume fiber intakes (HR = 0.55, 95% CI: 0.32-0.95; $p = 0.04$). In contrast, there was not significant association between PCa risk and cereal fiber ($p = 0.7$). Surprisingly, in the study of Bosire et al.¹⁴, the legume construct of the alternate MeDi score was positively associated with increased risk of fatal PCa. The authors explained that it was possible that consumption of legumes in their population was associated with higher intake of other foods, for example, red and processed meat. No other studies have reported similar findings, and there is no plausible explanation for this association.

Moderate to low intake of dairy products

Mediterranean eating also typically includes low to moderate consumption of dairy products. The positive association between dairy product intake and PCa has been reported in several studies, including the European Prospective Investigation into Cancer and Nutrition⁴⁴ and studies in Canada⁴⁵ and Japan⁴⁶. However, the results of 2 meta-analyses of the relation between dairy product intake and PCa provided conflicting conclusions: one showed a significantly positive association⁴⁷ and the other (supported by the National Dairy Council) showed an overall null association⁴⁸.

In a recent study, Song et al.⁴⁹ investigated the association between intake of dairy products and the incidence and survival of PCa during a 28-years follow-up. They conducted a cohort study in the Physicians Health Study (n = 21,660) and a survival analysis among the incident PCa cases (n = 2806). The intake of total dairy products was associated with increased PCa incidence (HR = 1.12, 95% CI: 0.93-1.35; >2.5 servings/d vs. 0.5 servings/d). In addition, in the survival analysis, whole milk intake remained associated with risk of progression to fatal disease after diagnosis [(HR = 2.17, 95% CI: 1.34-3.51)].

Moderate intake of wine

MeDi is associated with moderate alcohol consumption, especially of red wine, usually at meals. Furthermore, alcohol intake is a modifiable lifestyle factor on the risk of prostate carcinogenesis, so the finding of a tiny association with this kind of cancer incidence could have a significant impact on public health. Red wine contains high concentrations of polyphenols, a potent antioxidant that is particularly prevalent in the skin and seed of grapes and may alter cell growth.

A 2010 review about alcohol consumption and PCa⁵⁰ concluded that moderate alcohol consumption, up to about three drinks per day, does not appear to influence PCa risk. However, heavy consumption may be associated with an excess risk for this disease. The level of risk at this level of exposure is modest and could be due to confounding of other causal factors or due to biases inherent in observational studies. These conclusions are in concordance with one previous epidemiologic review⁵¹. Related to these, we can also find different meta-analyses. Most of them did not see any evidence of a significant relationship between moderate alcohol consumption and PCa⁵²⁻⁵⁴. Nevertheless, a Fillmore et al.⁵⁴ meta-analysis suggests a statistically significant positive association between number of drinks per day and PCa (OR = 1.158, 95% CI: 1.051 - 1.263).

While many epidemiologic studies have investigated associations between alcohol consumption and PCa with largely null results, fewer have investigated associations between specific alcoholic beverages, such as red wine, and PCa⁵⁵. Some of these cohort and case-control studies did not find any appreciable role for moderate red wine drinking on the risk of PCa⁵⁵⁻⁶⁰. A 2005 case-control study involving 753 cases and 703 controls found an inverse association with risk of PCa for level of wine consumption, particularly for red wine (OR = 0.94, 95% CI: 0.90-0.98), especially in more aggressive forms of the disease⁶¹. It accords with a previous study which had a slight but not significantly divergence between abstainers from wine⁶² and subjects who drank 1–13 glasses of wine/week (RR = 1.13, 95% CI: 0.84-1.53) or more than 13 glasses of wine/week (RR = 0.92, 95% CI: 0.42-1.99) respectively. In contrast, few other studies were found concluding that consumption of total alcohol is associated with an increase in the risk of PCa, but did not find any association with red wine⁶³⁻⁶⁵.

Finally, we can also find one study carried out in three human PCa cell lines⁶⁶: the hormone-sensitive LNCaP cell line, possessing a high number of functional androgen receptors; PC3 cells, possessing non-functional androgen receptors; and DU145 cells, containing no androgen receptors. The effect of red wine on the proliferation of these cell lines after five days of incubation was a dose-dependent inhibitory effect on cell proliferation for all cell lines tested (LNCaP and PC3 cells were more sensitive than DU145 cell to the

effect of wine). At wine dilutions of 1:50 (comparable to the ingestion of 1 liter), the maximum effect of wine was found (inhibition >80%). However at higher concentrations, a reverse effect was observed, indicating that other substances, different from the examined polyphenols, might interfere with this growth effect or that high concentrations of specific polyphenols could act as growth stimulants, rather than inhibitors.

Conclusion

Epidemiological studies have suggested that MeDi may play a role in PCa etiology because of the wide variation in its incidence across the European Union. There is strong evidence supporting associations between foods and bioactive components that are typical of a Mediterranean eating pattern and reduced PCa risk; therefore it could be argued that a combination of these foods, as would be achieved in a Mediterranean eating pattern, would have synergistic effect providing greater protection against PCa. However, there are few studies that have assessed the effect of the MeDi on cancer prostate incidence. Recent data do not support associations to adherence to a MeDi and risk of PCa or disease progression. However, Mediterranean eating pattern after diagnosis of nonmetastatic cancer was associated with lower overall mortality. Hence, relations between Mediterranean dietary patterns and PCa are still inconclusive and merit further investigations. Further large-scale studies are required to clarify the effect of MeDi on prostate health, in order to establish the role of this diet in the prevention of PCa.

Declaration of interest

The authors have no relevant interests to declare.

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