

Narrative review of Mediterranean diet in Cilento: longevity and potential prevention for prostate cancer

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The Mediterranean diet (MD) represents an important lifestyle able to act as a preventive intervention against chronic degenerative diseases such as diabetes, tumors, autoimmune diseases, neurological disorders, and cardiovascular disease.¹ Indeed, in the past decade, the scientific community has performed several *in vivo* and *in vitro* studies to understand how the different macronutrients and micronutrients present in the different foods consumed in a MD could have beneficial effects on human health.²⁻⁴

Ansel Keys demonstrated the cardioprotective role of MD between the years 1950 and 1970 in a first observational study in which he showed that cultural phenomena, diets and activities, are the main causes of the different rates of heart disease. Ansel Keys' Seven Country Study highlighted how MD affected a significant reduction in atherosclerotic processes by significantly reducing the rate of cardiovascular diseases.⁵ Throughout the 1990s, further clinical studies demonstrated MD favorable influences on the risk of metabolic syndrome, obesity, type 2 diabetes mellitus, cancer, and neurodegenerative diseases.⁶⁻⁸ More recently, the PREDIMED trial provided strong evidence that a vegetable-based diet such as MD can be a sustainable and ideal model for cardiovascular health.⁹

How diet affects cancer outcomes or prevention is also of great interest to patients, but there is a lack of clear evidence on how diet interacts with therapy and affects tumor growth. The study of tumor cell metabolism led researchers to understand

how different nutrients can support or modulate growth and proliferation through the interaction between cellular intrinsic factors (neoplastic metabolic shift) and extrinsic factors (antioxidant effects, influences on hormonal metabolism, etc.).

Prostate cancer (PCa) is the second most common cancer in men, with nearly a million new cases diagnosed worldwide per year. Recently, several authors provided evidence that western diet patterns (WD), characterized by a high loading of red meat, processed meat, sweets and refined carbohydrates, is significantly associated with an increase in PCa risk.^{10,11} According to Fabiani *et al.*, a linear trend is evident between the adherence to the WD and PCa risk.¹⁰ Conversely, high adherence to the MD was inversely associated with the likelihood of having PCa in Italian men.¹² In addition, the Mediterranean eating pattern is associated with lower PCa aggressiveness.¹³

A study conducted in Europe showed that southern countries, which follow a MD, show a reduced incidence and mortality of PCa when compared with the other 37 European countries involved in the study.¹⁴ This epidemiological observation makes strong hypotheses about the influence of MD, based on a high intake of vegetables, fruits, nuts, legumes, cereals and lean fish, moderate consumption of alcohol and low amounts of milk and red meat, on the reduction of PCa risk. The main features of all large studies (we considered studies with at least 1000 participants) that

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Table 1. General study characteristics of included studies that examined the association between MD and PCa risk.


Population	Study design	Period of follow-up	Significant findings
Bosire <i>et al.</i> ²¹ (<i>n</i> = 293464)	Cohort	8.9 years	No significant association between MD and total prostate cancer
Castelló <i>et al.</i> ²² (<i>n</i> = 1277)	PCC	NA	High adherence to a MD could have a protective effect against more aggressive and more advanced PCa
Kenfield <i>et al.</i> ²³ (<i>n</i> = 47867)	Cohort	23.3 years	A higher MD score was not associated with risk of advanced PCa or disease progression. Greater adherence to the MD after diagnosis of non-metastatic PCa was associated with lower overall mortality
Lavalette <i>et al.</i> ²⁴ (<i>n</i> = 41543)	Cohort	2009–2017	Higher adherence to dietary recommendations proposed by the World Cancer Research Fund/American Institute for Cancer Research could significantly contribute to cancer prevention
Möller <i>et al.</i> ²⁵ (<i>n</i> = 1108)	PCC	NA	No association between adherence to the MD and PCa risk
Muller <i>et al.</i> ²⁶ (<i>n</i> = 14627)	Cohort	13.6 years	No association between any dietary pattern and prostate cancer risk overall
Schulpen and van der Brandt ²⁷ (<i>n</i> = 58279)	Cohort	20.3 years	MD adherence was not associated with decreased risks of advanced prostate cancer

MD, Mediterranean diet; *N*, no. of controls/participants; NA, not applicable; PCa, prostate cancer; PCC, population-based case-control.

examined the association between MD and PCa risk are summarized in Table 1. Evidence from Schwingshackl *et al.*¹⁵ suggests an inverse association between adherence to a MD and cancer mortality and the risk of several cancer types, but findings from more recent meta-analyses failed to reveal a protective effect of MD on PCa risk.^{16,17} It should be underlined that a variety of non-dietary factors also appear to affect PCa progression.¹⁸ For example, physical activity and maintaining a healthy body weight appear to lower the risk of PCa progression (Table 2). Nevertheless, the current tools available to assess the population's adherence to the MD consider mainly food issues and virtually no lifestyle components.¹⁹ In this regard, MD is not only about food as it is a way of life and, first of all, the MD was associated with regular and intense physical activity, reaching a perfect balance with the energy intake.²⁰

However, a vast rural area of southern Italy in the Campania region, namely Cilento, is considered the cradle of the MD²⁸ (Figure 1(a)). According to the Italian Institute for Statistics (ISTAT) there are 183 centenarians in the Cilento and Diano's Vallo territories, basing on the data up to January 2016.²⁸ This area is very different from other regions of Italy, both for cultural traditions and for the availability of typical products,²⁹ resulting in a unique traditional cooking style. For example, a very common soup, known as 'minestra terrana', is made by 12 wild plant species: *Borago officinalis* and aerial parts of *Bellis perennis* L., *Cichorium intybus* L., *Crepis bursifolia*, *Crepis leontodonoides*, *Hypochoeris cretensis*, *Lapsana communis* L., *Reichardia picroides*, *Sonchus asper* (L.) Hill., *Sonchus oleraceus* L., *Taraxacum laevigatum* (Willd.) DC., *Taraxacum officinale* Weber.²⁹ Further typical recipes of the Cilento

Table 2. Main risk factors and risk of prostate cancer progression.

	★★★★	BMI, smoking
	★★★	Dairy/calcium
	★★	Processed red meat, eggs, poultry (with skin), animal fat, selenium supplementation
	★	Coffee, soy, tea
	★★★★	Cruciferous vegetables, vegetable fat, tomatoes/lycopene, fish
	★★★★	Physical activity

Adapted from Peisch *et al.*¹⁸

The number of stars indicates the strength of the evidence, not the magnitude of effect. One star means that the association is supported by at least one well-designed observational cohort study while three stars mean that the relationship between the risk factor and outcomes among men with prostate cancer is most likely real. The red arrow and the green arrow mean increased risk and decreased risk, respectively.

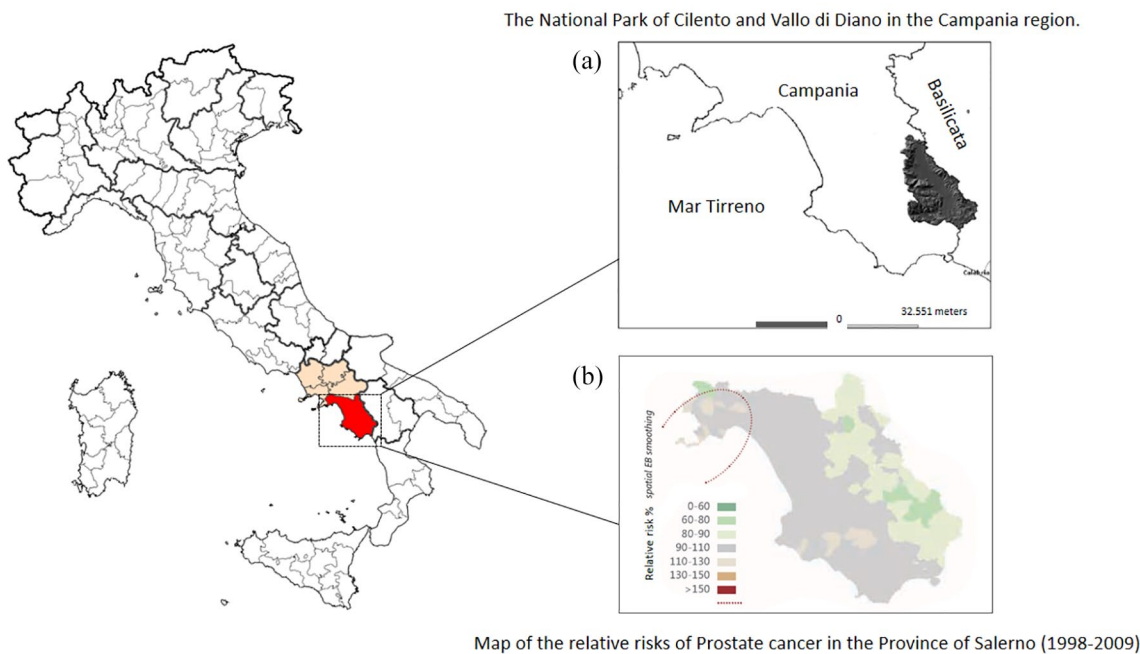


Figure 1. In the left panel there is a representation of Italy with all regions (delimited with a double black line) and the provinces of each region. The red color identifies the province of Salerno while the other provinces of Campania are depicted in lighter red. In the right panel, the dark grey area identifies the National Park of Cilento and Vallo di Diano in the Campania region (a) while immediately below (b) there is a map of the relative risks of prostate cancer in the Province of Salerno (1998–2009). In (b) the orange and red areas are associated with a higher risk of disease than the provincial average risk, the green areas instead show a lower risk than the provincial average risk.

culinary tradition are available in an interesting book recently published by Calella and Siervo.³⁰

In addition, the strong influence of the Mediterranean climate has allowed the growth of a great variety of vegetables, fruits, legumes and the production of olive oil and wine used in daily meals.

The study of this area prompted researchers to investigate further by highlighting the presence of a high number of long-living individuals (LLIs) among the resident population. The presence of centenarians in these rural areas has been associated with genetic factors and lifestyles that still mark the lives of these people. The influence of

the macro and micronutrients consumed daily would seem to have contributed to a protective effect.²⁸ The study of the oxidative status of the nonagenarian and centenarian population in Cilento showed a slight increase in reactive species of oxygen (d-ROMs) [324.1, standard deviation (SD) 79.4] and values within limits for anti-ROMs 1 and 2 (234.4, SD 99.7 and 1188.8, SD 433.3), reflecting a good overall control of the oxidative balance.³¹ These data suggest that genetics, Mediterranean lifestyle (diet and psychosocial habits), could be involved in maintaining this balance unaltered over time, allowing for healthier aging.³²

Olive oil is the main component of the MD and one of the main sources of antioxidants. In particular, a species of olive tree grows in the Cilento Regional Park, *Olea europaea*, which attributes the protected designation of origin to the oil produced.³³ The olive oil extracted from *Olea europaea* contains not only oleic acid but also numerous substances capable of playing an important antioxidant role. These components include alpha-tocopherol and carotenoids, which have been widely studied, and several phenolic compounds, such as tyrosol and hydroxytyrosol, which represent the major share of antioxidants in olive oil as metabolites of the oleuropeins, phytosqualene, secoiridoids, phytosterols, and lignans.³⁴

All these components appear to play a protective role against the initiation, promotion, and progression of the neoplastic and inflammatory process.

The daily consumption of at least two servings of fruit and vegetables, respectively, foods rich in vitamins, minerals and various polyphenols is at the base of the MD pyramid. Among the many polyphenols, lycopene and quercetin are substances that have an important effect on tumors.

Lycopene is a terpene contained in tomato, determining its red pigmentation. It has a strong antioxidant effect, higher than other compounds such as β -carotene and lutein. Findings from an experiment conducted in prostate cancer animal models have shown that lycopene has strong anti-cancer effects.^{35,36} Other studies also suggested that a high intake of dietary lycopene inhibited neo-angiogenesis with less blood vessel formation in PCa,^{37,38} and several authors confirmed that higher dietary and circulating lycopene

concentrations are inversely associated with PCa risk.^{37,39,40}

Quercetin is a naturally occurring flavonol that is abundant in vegetables and fruit, in particular in apples and onions.⁴¹ Quercetin and its glycosylated form isoquercetin are remarkably safe for human consumption.⁴² Isoquercetin has also been developed as a pharmaceutical agent in prostate cancer; quercetin may exert potent preventive activity,⁴³ by virtue of its strong anti-oxidant properties,⁴⁴ although this hypothesis remains to be demonstrated in large, population-based epidemiological studies. Also, quercetin has been found to synergize with several agents approved against prostate cancer, including novel hormonal therapies⁴⁵ and chemotherapy agents,⁴⁶ and may represent an attractive agent in those patients who remain asymptomatic despite progressing on docetaxel⁴⁷ and enzalutamide.⁴⁸

The relative contribution of each compound to human health remains unclear because of the co-presence of other beneficial components such as fiber and no-antioxidant molecules, which may mask or render extremely difficult the determination of the exact effect of individual compounds. Anyway, it would be plausible that combining these bioactive elements, as in a MD pattern, would have a synergistic effect providing protection against PCa.⁴⁹ Interestingly, some authors described the MD as an epigenetic diet because the epigenome has been identified as the primary goal of modulating gene expression related to these bioactive compounds.^{50,51} For example, quercetin was able to inhibit the proliferation, invasion and migration of cancer cells due to suppression of Janus kinase 2 (JAK2).⁵² Many studies have shown the ability of resveratrol in modulating DNA methylation in several genes involved in cancer.⁵³ In this context, the role of several bioactive components of the MD in modulation of epigenetic mechanisms was described in depth by Divella *et al.*⁵¹

Epidemiological data from the province of Salerno (data provided by the local health authority and collected in the cancer registry) demonstrate the lower risk of PCa in this zone compared to the neighboring areas of the province of Salerno (Figure 1(b)), suggesting a great protective role of the MD against PCa. Cilentos' nonagenarians seemed to have good cognitive status when compared to younger cohabitants aging 50–65 years, without significant differences in

oxidative stress markers or apolipoprotein E (ApoE) genotype attributing these results to an optimal adherence to the MD, although other lifestyle factors and positive personality traits may also contribute to their healthy aging.³² In this scenario a recent study attempted to identify genes/miRNAs involved in life span and health span in LLIs from Cilento.⁵⁴ In particular, the authors evaluating the circulating mononuclear cells (MNCs) transcriptome, found that both BPIFB4 and CXCR4 expression in MNCs were powerful classifiers of healthy aging in LLIs.⁵⁴ Also other typical Mediterranean habits, such as cooking and having meals together with the family, might be related to an overall health benefit, including decreases in PCa risk and progression. It is clear that the incidence and progression of PCa is multifactorial but currently a strong theoretical rationale supports the adoption of the MD in reducing the onset of PCa.^{49,55} According to Fantus *et al.*⁵⁶ men who adhered to a MD had lower serum testosterone in a large, nationally representative patient sample.⁵⁶ This observation is very interesting given that clinical evidence implicates testosterone in the aetiology of PCa. Several authors have already reported the association of lower serum testosterone concentrations with high-grade PCa and a higher stage at presentation.^{57–60} In 2018, the first large-scale prospective evidence supporting an association between low free testosterone concentrations and PCa risk was published by Watts and co-workers.⁶¹ Mechanistically, when circulating free testosterone concentrations are very low, reduced androgen receptor signalling probably led to a reduction in PCa risk,^{62–64} while variation across the normal range of circulating free testosterone serum levels may not be related to a PCa risk. Nevertheless, more research is required to clarify whether the association is causal or due to detection bias.

In conclusion, several authors have evaluated the effect of the MD on PCa incidence, obtaining mixed results.^{21–27} Hence, the beneficial effects of several MD nutrients on PCa are still inconclusive and merit further investigations. Recently, findings from Gregg *et al.* have shown that adherence to the basic principles of the MD may lower the risk of Gleason grade progression among US men with localized PCa on active surveillance.⁶⁵ Further studies are needed to verify patient and cancer-specific effects of MD adherence in men with early-stage PCa. In addition, future studies

should evaluate MD adherence with tools that include not only food consumption but also the evaluation of lifestyle factors and cultural subtexts. Moreover, further randomized clinical trials of MD in Cilento in active surveillance, or large population datasets from Italy to show a clear association between lycopene and stage are needed.


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