

Impact of Mediterranean Diet on Cancer: Focused Literature Review

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Abstract. *Background:* Cancer is a major public health problem worldwide, and the number of incident cases increases every year expected to reach 17.1 million a year by 2020. There is evidence that people who adhere to the Mediterranean Diet (MediD) have lower incidence of cancer. However, cancers' location and culture studies seem to affect the MediD impact. We aimed to review these discrepant findings. *Materials and Methods:* A critical review from a focused literature search was conducted. A literature search of controlled trials from: EMBASE (1970-), MEDLINE (1950-) and PsycINFO (1960-) was undertaken. Two authors (DF and YB) independently extracted the data. *Results:* Out of 785 abstracts identified only 583 publications focused solely on MediD and cancer. Of these, 46 were clinical trials published since 2007. Twenty-eight trials with a total of 570,262 participants are included in accordance with inclusion criteria. Only four reported the MediD does not reduce the risk of cancer. Of the negative studies, three were undertaken in non-Mediterranean populations. Cancers of the digestive tract were studied in 11 studies. Except for pancreatic cancer, all other sites along the digestive tract demonstrated significantly reduced rate with the MediD. *Conclusion:* The MediD is associated with reduction in overall cancer rates as well as significantly lower rates of digestive tract cancers. These effects may be accentuated in the Mediterranean countries themselves. Further studies are needed to support or refute the effects of the MediD on other cancer types.

Cancer is a major public health problem worldwide, and the number of incident cases increases every year. According to

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GLOBOCAN, 14.1 million incident cases were recorded in 2012 (1). The World Health Organisation estimates that these numbers will grow to 17.1 million a year by 2020 (2). There is evidence that people who adhere to the Mediterranean Diet (MediD) have lower incidence of cancer (3, 4).

MediD includes plant foods such as fruits, vegetables, cereals, legumes, nuts, seeds, and olive oil. The diet also contains dairy products with recommended low consumption of milk and high consumption of cheese and yoghurt, moderate consumption of fish, eggs, low amounts of red meat consumption, and low to moderate consumption of wine, mainly with meals. (4).

It is important to recognise the different relationships between MediD and cancer across studies and types of cancer. For example, there is evidence that MediD can mediate the effects of smoking on colorectal cancer (5), and is associated with more than 50% reduction in oropharyngeal, oesophageal and laryngeal cancer risks (6). Moreover, MediD is associated with lower risk of breast cancer amongst postmenopausal women (7). However, there is no association between MediD and breast cancer amongst premenopausal women (7).

Therefore, there is a need for a critical review of the literature in order clarify the effects of MediD on cancer overall and across studies, recognise gaps in the research, and gather insights into how we might design interventions for the prevention of cancer.

Materials and Methods

Approach to reviewing process. This was based in part on the approach recently advocated by Catts and O'Toole (8). Briefly, the clinical issue reviewed was selected because the authors considered it decidedly relevant to clinical practice and likely to impact on health outcomes and its contentious nature is reflected in divergences across guidelines and clinical practice. This critical review results from a of focused literature search. Although a systematic review would have been desirable, a critical review approach was the feasible way to integrate the literature. Selection of material was strongly weighted by relevance.

The following bibliographic databases: EMBASE (1970-) and MEDLINE (1950-) were searched. Bibliography of all studies and relevant reviews were screened. Two review authors (DF and YB) independently extracted the data.

Inclusion criteria for studies to be analysed in the present review were: (1) controlled trials (CTs), (2) Mediterranean diet the only lifestyle “intervention,” (3) use of rating scales to quantify adherence to the MediD, (4) sample size >200, (5) OR (Odds Ratio) or HR (Hazard Ratio) reported as outcome and (5) publication in the last 10 years. Exclusion criteria: (1) review or meta-analysis (2) cancer not primary outcome and (3) number of cases not reported.

Results

Our search identified 785 abstracts, but only 583 publications focused solely on the MediD and cancer. Of these 46 were clinical trials published since 2007.

In the present review 28/46 trials with a total of 570,262 participants are included in accordance with inclusion criteria. The European Prospective Investigation into Cancer and Nutrition (EPIC; 9) was counted only once in contributing to the total number of participants in the present review. Due to clinical heterogeneity, few direct comparisons were possible. The main outcome in the published studies was OR or HR. See Table I for details of studies reviewed.

The first study to assess the effects of the MediD was published in 1985. The authors reported on variations in cancer mortality in Italy suggesting:” It is conceivable that dietary factors may also explain some of the differences. However, at present, there is no obvious general explanation for this quite peculiar geographical distribution of cancer mortality within a single country...” (10). Since then hundreds of studies focused on the role of the MediD in reducing cancer rates.

In the present review of 28 studies analyzed and 4 of these studies reported that adherence to the MediD does not reduce the risk of cancer (6-9, 13, 14, 24-43). It is important to note that of the negative studies three were undertaken in non-Mediterranean populations; USA, Sweden and Holland (11-14).

Cancers of the digestive tract were studied in 11 different studies including nasopharyngeal cancers, gastric, pancreatic and colorectal. It is of interest to note that except for pancreatic cancer all other sites along the digestive tract demonstrated significantly reduced rate of cancers with adherence to the MediD. The largest effect (smallest OR) in the present analysis was indeed for oral cavity and pharyngeal cancer (OR: 0.20).

In addition, breast cancer studies are the largest single cancer type studied in the present analysis. There were 7/28 studies focusing on breast cancer of which two were based on data from the EPIC project. In two of the seven studies non-significant reductions in OR or HR were reported, in three studies reduction in risk was minimal (OR=0.88-0.94). Moreover, in two of the studies the significant effects of the

MediD were demonstrated only for estrogen receptor negative tumors.

Discussion

“Cancer is a preventable disease that requires major lifestyle changes” declared Anand and colleagues in 2008. Each year 12.7 million people discover they have cancer and 7.6 million people die from a disease commonly believed to be preventable. The great majority of cancers have their roots in the environment and lifestyle. Lifestyle factors for which abundant public and scientific awareness is raised include: cigarette smoking, diet, alcohol, sun exposure, environmental pollutants, infections, stress, obesity, and physical inactivity (15). The evidence indicates that of all cancer-related deaths, as many as 30-35% are linked to diet (16). In a more recent global review the population attributable fraction - the epidemiological measure that quantifies this potential reduction in incidence - was reported for most cancer sites. Studies distribution was not uniform, with many articles reporting cancer population attributable fractions for and tobacco, but fewer reporting population attributable fractions for dietary factors (17, 18). In the present review, we aimed to assess the benefits attributed to the MediD in reducing the risk of developing cancer.

As seven of the studies herein analyzed are from the EPIC database that is the largest database available to date focusing on “cancer and nutrition...” we need to briefly recap the principle components of the EPIC project. Conceptualized and initiated in the early 1990’s the EPIC study was originally conceived as a multi-centre prospective cohort study designed to investigate the relation between diet, nutritional and metabolic characteristics, various lifestyle factors and the risk of cancer. The study was based in 22 collaborating centres in nine European countries and includes populations characterized by large variations in dietary habits and cancer risk.

It was planned to include around 400,000 middle-aged men and women and it was expected that about 23,000 cancer cases will be identified during the first 10 years of follow-up (19). By now the EPIC study cohort includes over half a million participants, from 10 countries in Europe recruited between 1991 and 2000 with a mean follow-up of almost 15 years (20). In the EPIC study the overall cancer risk was found to be reduced with an HR of 0.88 when 25,623 cancers were analyzed.

The present analysis supports previous reports on the association between the MediD and reduction in overall cancer rates as well as reductions in digestive tract cancers. Findings are not as clear-cut when data is derived from non-Mediterranean countries or for cancer sites other than the digestive tract. The reproductive hormonally affected cancers (breast, endometrial and prostate) were reported to be

Table I. Summary of studies reviewed.

References	Study design	Sample size: cases and controls	Cancer type	Outcome	Comments
Stojanovic <i>et al.</i> (24)	Case-Control	446	Gastric	OR: 0.70	
van den Brandt & Schulpfen (14)	Case-Cohort	3,986	Breast	OR: 0.94 NS	Significant effect for ER negative tumors
Molina-Montes <i>et al.</i> (13)	Prospective cohort study	865	Pancreatic	HR: 0.99 NS	EPIC study
Turati <i>et al.</i> (25)	Case-Control	792	Nasopharyngeal	OR: 0.66	
Rosato <i>et al.</i> (26)	Case-Control	10,549	Colorectal	OR: 0.52	
Giraldi <i>et al.</i> (27)	Case-Control	933	Head and Neck	OR: 0.61	
Hodge <i>et al.</i> (28)	Case- Series	403	Lung	HR: 0.64	Especially for current smokers
Toledo <i>et al.</i> (29)	Case-Control	4,152	Breast	HR: 0.32	The PREDIMED study
Filomeno <i>et al.</i> (30)	Case-Control	5,079	Endometrial	OR: 0.43	
Castello <i>et al.</i> (31)	Case-Control	2034	Breast	OR: 0.56	Significant effect for ER negative tumors
Filomeno <i>et al.</i> (6)	Case-Control	2,846	Oral cavity and pharyngeal	OR: 0.20	
Mourouti <i>et al.</i> (32)	Case-Control	500	Breast	OR: 0.91	
Grosso <i>et al.</i> (33)	Case-Control	1014	Colorectal	OR: 0.46	
Praud <i>et al.</i> (34)	Case-Control	3627	Gastric	OR: 0.78	
Buckland <i>et al.</i> (35)	Prospective cohort study	477,312	Bladder	HR: 0.84	EPIC study
Kenfield <i>et al.</i> (36)	Prospective cohort study	4538	Prostate	HR: 0.78	
Idilbi <i>et al.</i> (37)	Case-Control	200	Overall cancers	OR: 0.4	
Bosetti <i>et al.</i> (38)	Case-Control	2,892	Pancreatic	OR: 0.57	
Bamia <i>et al.</i> (39)	Prospective cohort study	4355	Colorectal	HR: 0.89	EPIC study
Möller <i>et al.</i> (12)	Case-Control	2,590	Prostate	OR: 1.07 NS	
Buckland <i>et al.</i> (40)	Prospective cohort study	335,062	Breast	HR=0.94	EPIC study. Significant effect for ER negative tumors. Premenopausal women NS. Postmenopausal women (HR=0.80).
Kontou <i>et al.</i> (35)	Case-Control	500	Colorectal	OR: 0.87	
Kontou <i>et al.</i> (41)	Case-Control	500	Colorectal	OR: 0.89	
Cade <i>et al.</i> (42)	Cohort Study	33,731	Breast	HR: 0.65	
Trichopoulou <i>et al.</i> (7)	Prospective cohort study	14,807	Breast	HR=0.88	EPIC study. Premenopausal women (HR=1.01). Postmenopausal women (HR=0.78).
Samoli <i>et al.</i> (43)	Case-Control	433	Upper Aerodigestive Tract	OR: 0.70	
Buckland <i>et al.</i> (9)	Prospective cohort study	485,044	Gastric	HR: 0.67	EPIC study
Benetou <i>et al.</i> (3)	Prospective cohort study	25,623	Overall cancers	HR: 0.88	EPIC study
Dalvi, Alison & Pamela (11)	Case-Control	949	Endometrial	OR=1.4	

EPIC, European Prospective Investigation into Cancer and Nutrition. NS, Not statistically significant.

positively and negatively associated with the MediD. It is of interest to speculate on the highly positive effects of the MediD in Mediterranean countries. There are possibly additional variables and confounders that differentiate between the populations studied. Recent reports support the assertion that culturally specific diets may positively affect health. Three examples emphasize this concept: Chilli consumption in China, the Nordic diet and Asian flavonoids. The frequency of spicy food intake has recently been

associated with a reduced risk of mortality in the Chinese population. A total 12,970 Chinese adults were followed for a median of 9 years. Chilli consumption was found to be inversely associated with the incidence of obesity (21). The Nordic Nutrition Recommendations were evaluated in a systemic manner to assess Health effects associated with foods characteristic of the Nordic diet. Based on 57 studies. There was suggestive evidence (low-grade) for whole grains protecting against colorectal cancer (22). The selection of a

particular food plant, plant tissue or herb emulates its flavonoid composition. The lower risk of colon, prostate and breast cancers in Asians, who consume more vegetables, fruits and tea than populations in the Western hemisphere do, raises the question of whether flavonoid components mediate this protective effect (23).

We conclude that the MediD is associated with reduction in overall cancer rates as well as significantly lower rates of digestive tract cancers. These effects may be accentuated in the Mediterranean countries themselves. Further studies are needed to support or refute the effects of the MediD on other cancer types.

Expert Commentary

The MediD has been researched and assessed for approximately 40 years and over 1,500 publications attest to the interest it ignites. Much of our knowledge about this diet has come from studying populations restricted in geographical distribution. The realization that the MediD is still rapidly evolving as a nutritional intervention to reduce cancer rates is important.

As we were reminded, 2017 marks the 20th anniversary of the publication of the results of the Dietary Approaches to Stop Hypertension (DASH) Diet Study. Despite the impressive results, numerous surveys have shown that the DASH diet is underutilized among the tens of millions of US citizens who have hypertension and prehypertension. If we do not wish the MediD to suffer the same setbacks that the DASH does increased emphasis on educating providers (both in training and continuing medical education) may be helpful. Leaders of the community of providers who are committed to public health, we all have a responsibility to continue to emphasize healthy lifestyle habits, including the MediD eating plan, to our colleagues and patients.

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