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Review Paper

Does adherence to the Mediterranean diet have a protective effect against active and passive smoking?

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SUMMARY

Objective: To investigate the existing evidence about whether adherence to the Mediterranean diet may have a role as an effect modifier of active and passive smoking on human health.

Study design: Review.

Methods: An overview of emerging evidence and published studies that cover the interaction between the Mediterranean diet and smoking.

Results: Both epidemiological and laboratory studies have shown that the Mediterranean diet has a protective effect against biochemical and molecular processes that lead to cancer, cardiovascular disease and respiratory illness. Based on the high daily intake of vitamins and antioxidants, the Mediterranean diet is comprised of a number of compounds that could alter certain outcomes related to smoking. Studies have indicated that certain diseases attributable to smoking, such as lung cancer, asthma and cardiovascular disease, are inversely associated with certain antioxidants and lipids.

Conclusions: The literature indicates that the existence of a partial interaction between adherence to the Mediterranean diet and the health effects of smoking is possible. Further research is needed to lead to a conclusive statement on this hypothesis.

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Introduction

Detrimental effects of active and passive smoking

Smoking is one of the largest causes of preventable death, and is expected to kill 1 billion people prematurely this century. Second-hand smoke (SHS) is another serious threat to public health, subsequent to tobacco use, and is a potent mixture of

carcinogens, volatile toxins and chemicals.^{1–3} It has been estimated that, worldwide, at least 1 billion adults are smokers and at least 700 million children breathe air polluted by tobacco smoke at home.⁴ SHS exposure is related to the ever-increasing frequency of diseases among children and adults, such as respiratory illness, asthma, otitis media, sudden infant death syndrome and vascular dysfunction, and predisposition towards cardiovascular disease and cancer.^{5–8}

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Moreover, although cardiovascular disease and chronic lung disease are generally the result of long-term processes, recent evidence shows that even brief SHS exposure appears to initiate mechanisms that contribute to their development.^{9,10}

Cigarette smoke contains free radicals and other oxidants in abundance. It has been estimated that each puff of a cigarette exposes the smoker to 10^{15} oxidative free radicals, a severe source of oxidative stress.¹¹ Additionally, the production of reactive oxygen species is further mediated through inflammatory processes induced by the toxins inhaled and absorbed during active and passive smoking.¹² The first line of response is that of antioxidant enzymes such as superoxide dismutase, catalase and glutathione peroxidase, which take advantage of the circulating levels of dietary antioxidants, a second line of defence against oxidative stress. These antioxidants are digested and enter the circulation, acting as a buffer against oxidative stress, and therefore could have a protective effect against antioxidant depletion.

An important issue for public health is whether or not the marked changes in the subjects' health are solely due to the harmful effects of cigarette smoke or to a combined effect of both the oxidative properties of cigarette smoke and the habitual dietary profile of smokers, which is generally lower in fruit and vegetable intake, and higher in alcohol and meat consumption compared with non-smokers.^{13–15} Moreover, it is likely that the cumulative effect of both the elevated oxidative stress and lower dietary intake of antioxidants is partially responsible for the negative impact of smoking on human health.

The Mediterranean diet and the smoking paradox

The Mediterranean diet became world renowned in the early 1960s through the Seven Countries Study, an epidemiological study with 16 cohorts in seven countries (Greece, Finland, Japan, former Yugoslavia, Italy, Holland, USA), which aimed to investigate the dietary and lifestyle factors related to the development of cardiovascular disease.¹⁶ As corroborated during the subsequent 10-, 25- and 40-year follow-up of the Seven Countries Study, the rural population of Crete was found to have among the lowest mortality rates for coronary heart disease and cancer, and this was attributed to their dietary and lifestyle habits.^{17,18} The traditional diet of Crete (i.e. the typical 'Mediterranean diet') is based on high intake of vitamins, fibre and antioxidants through the consumption of olive oil, wild greens, fruits, wholewheat bread, legumes, walnuts, almonds and snails, supplemented with rare to moderate consumption of red meat, fish and dairy products.¹⁹ In addition, mono-unsaturated fat (through the extensive consumption of olive oil) accounted for 29% of the daily calorie intake, while saturated fat accounted for 8% of total energy intake.²⁰

Furthermore, after following up the 12,763 men of the Seven Countries Study for 25 years, lung cancer mortality was found to be higher in Northern European and Northern American cohorts compared with Southern European and Japanese cohorts,²¹ while absolute lung cancer mortality was positively associated with average dietary intake of saturated fat, which was lowest in both the Mediterranean and the Japanese diet, both known for their high antioxidant and low saturated fat profile.^{22,23} Specifically, the researchers

hypothesized that saturated fat may play a role in the cross-cultural variation in lung cancer mortality, either independently or by effect modification, despite the fact that smoking habits were similar across countries and regions.

Aims and scope

Currently, one of the emerging issues in environmental toxicology is evidence which suggests that antioxidant micronutrients and related bioactive compounds common in fruit and vegetables may ameliorate the toxicity of environmental chemicals and impact disease development, and it has been hypothesized that adherence to the Mediterranean diet may function in such a way.^{23,24}

Taking the above scientific facts and epidemiological findings into account, the authors aimed to investigate the existing evidence that could indicate whether adherence to the Mediterranean diet may have a role as an effect modifier of active and passive smoking on human health.

Active/passive smoking, cardiovascular disease and the Mediterranean diet

Active and passive smoking and the risk of cardiovascular disease

Active cigarette smoking and exposure to SHS are strongly associated with vascular dysfunction and atherosclerosis, and impact all phases of atherosclerosis from endothelial dysfunction to acute clinical events.^{25,26} Cigarette smoke can promote atherosclerosis, in part, by its effects on the lipid profile of active and passive smokers. Smoking decreases plasma high-density lipoprotein (HDL) levels, and alters HDL:low-density lipoprotein (LDL), HDL:triglycerides and HDL:total cholesterol in both animal models and humans.^{25,27} It is interesting to note that lipid peroxidation among young smokers is noted, even after controlling for dietary intake. Cigarette smoking also increases the oxidative modification of LDL, with circulating products of lipid peroxidation and levels of oxidized LDL found to be significantly increased in both active and passive smokers.^{27–29} This oxidized LDL may enter the arterial endothelial wall, leading to the attraction of macrophages, lymphocytes and, subsequently, paracrine factors that cause platelet accumulation and initiation of foam cells. This is the first step in developing an atherosclerotic plaque.³⁰ Additionally, it has been hypothesized that cigarette smoke alters catecholamine release and thus fatty acid release, which in turn increases LDL and very-low-density lipoprotein (VLDL) concentrations, and also contributes to lowering circulating HDL levels.³¹

Interaction between adherence to the Mediterranean diet and the cardiovascular factors influenced by active and passive smoking

In contrast to the above, randomized controlled trials have shown that adherence to the Mediterranean diet has a beneficial effect on circulating oxidized LDL levels, a factor that

could possibly counter balance the increase in oxidized LDL molecules induced by exposure to tobacco smoke.³² Epidemiological and clinical evidence have convincingly shown that dietary habits are the central mediator of circulating lipids.^{33,34} The differences in dietary fat intake are clearly apparent when comparing the Mediterranean diet with a more Westernized diet. Although the fat percentage is similar in both diets, it differs dramatically in that the Mediterranean diet is rich in mono-unsaturated fatty acids, such as oleic acid, but very low in saturated fat. Such a diet has the ability to reduce the levels of circulating LDL and VLDL, while increasing beneficial HDL.³⁵ Indeed, follow-up studies, such as the Lyon Secondary Prevention Heart Study on patients with cardiovascular disease, indicated that adherence to a Mediterranean-style diet was more beneficial than the American Heart Association's recommended diet and other pharmaceutical interventions.^{36,37} Additionally, olive oil is high in mono-unsaturated fatty acids and, as proven in numerous studies, plays an important role in the Mediterranean diet and contributes significantly to an increase in the circulating levels of HDL.^{19,20,38}

It has been stated that another important factor in the traditional Mediterranean diet of Crete is the ideal omega-6/omega-3 fatty acid ratio of 2–1:1, in opposition to that of Western cultures which have a ratio of approximately 15:1 for Northern Europe and 17:1 for the USA.^{39,40} These dietary omega-3 fatty acids are associated with lower prevalence of hypertension and lower systolic blood pressure, hyperlipidaemia and inflammation.^{41,42} These beneficial effects may be mediated through several distinct mechanisms, including alterations in cell membrane composition and function, gene expression or eicosanoid production, while studies reveal that they play a role in nerve conduction velocity due to the incorporation of omega-6 fatty acids in membrane phospholipids.⁴² In contrast, smoking and SHS exposure have a significant impact on the levels and interaction between omega-3 and omega-6 polyunsaturated fatty acids and can alter their metabolism.⁴³ As the dietary intake of alpha-linolenic acid (an omega-3 fatty acid) is inversely related of inflammatory markers (reflecting lower levels of inflammation and endothelial activation), it is possible to partially explain the role of this fatty acid in preventing cardiovascular disease due to smoking.⁴⁴ Moreover, the Mediterranean diet of Crete is abundant in wild greens, a rich source of both essential omega-3 fatty acids and antioxidants, especially during days of fasting.^{45,46} The periodical vegetarian diet observed during the approximately 180 days of fasting of the Greek Orthodox Church leads to an even more favourable lipid profile as fasters are generally reported to have lower intake of dietary cholesterol, total and saturated fat, protein and calcium, and higher intake of dietary fibre, folate, iron and carbohydrates during fasting periods compared with non-fasting periods.⁴⁷ This high fruit and vegetable intake also leads to an increase in vitamin and antioxidant intake with additional protective properties. Human health benefits from high levels of antioxidant vitamins, such as vitamin C, beta-carotene and lutein, that inhibit the oxidative process of LDL cholesterol into its atherogenic forms, and therefore preserve endothelial function and prevent the development of atherosclerosis and coronary heart disease.^{48–50}

Active/passive smoking, the Mediterranean diet and cancer

Active and passive smoking and the risk of cancer

The causal relationship between exposure to active and passive smoking and cancer is well acknowledged.³ It is also common knowledge that there is no lower threshold for tobacco carcinogenesis between the two types of smoking, either regarding lung cancer or tumours in other tissues that are indirectly exposed. Carcinogens absorbed in the lung are distributed throughout the body and have been proven to create or aggravate tumourgenesis.^{51,52} Such tobacco-specific carcinogens and their urinary metabolites, such as 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone, have been found to be consistently elevated in both active and passive smokers, and also indicate the causal link between exposure and lung cancer.³ In addition to the toxins and carcinogens incorporated in tobacco smoke, the gas phase, as mentioned above, exposes the smoker to more than 10^{15} free radicals per puff.¹¹ These oxidative free radicals (e.g. superoxide, hydroxide radical, nitric oxide and reactive oxygen) lead to oxidative injury on membrane lipids and proteins and DNA via various molecular pathways, leading to increased DNA damage and oxidative stress.^{7,8} These higher levels of both exogenous and intracellular produced free radicals can mediate signal transduction and trigger inflammation, cellular apoptosis and necrosis.⁵³

The interaction between adherence to the Mediterranean diet and the carcinotoxicity of active and passive smoking

Unlike cigarette smoking as an obvious risk factor for carcinogenesis (as it can be prevented simply by avoiding smoking), dietary habits and improvements in the balance of meals and meal portions cannot be easily explained due to their extreme complexity. A plethora of research and reviews exist on the role of the Mediterranean diet against cancer and its effect on overall mortality. One of the most recent meta-analyses is that of Sofi *et al.*,⁵⁴ who investigated a total of 12 cohorts and approximately 1.5 million subjects.⁵⁴ According to their results, adherence to the Mediterranean diet was associated with a significant reduction in overall mortality and the incidence of mortality from cancer. Similar findings were reported earlier by De Lorgeril *et al.* based on a randomized control trial.⁵⁵

Both toxicological and epidemiological evidences support the fact that dietary intake of fatty acids may alter the prevalence of cancer among populations that adhere to the Mediterranean diet.^{18,39,56} Dietary omega-6 fatty acids have also been shown to possess effective tumouricidal properties, when taken in accordance with their recommended daily intake, against prostate,⁵⁷ breast⁵⁸ and pancreas tumours.⁵⁹ Additionally, in mice, essential omega-3 fatty acids have been found to slow the growth of various types of cancers, including lung, colon, mammary and prostate.⁶⁰ Epidemiological data have indicated that a Mediterranean-style diet has a protective effect against the development of colorectal adenomas, with the strongest protective effect found among current smokers.⁶¹ Intake of red meat and processed meat,

which is also significantly reduced in populations that adhere to the Mediterranean diet, has been found to be independently associated with an increased risk of lung cancer, and strongly correlated with the development of adenocarcinomas and squamous cell carcinomas among smokers and non-smokers.⁶² On the contrary, a different interaction between smokers and non-smokers has been noticed with regards to the role of certain flavonoid compounds, such as epicatechin, catechin, quercetin and kaempferol, which have been found to be associated inversely with lung cancer among tobacco smokers but not among non-smokers, a fact that could indicate their possible protective role against tobacco smoke.⁶³

As with the cardiovascular protective effects of the Mediterranean diet, its protective role against cancer can also be attributed to the high consumption of olive oil, possibly the most characteristic descriptor of the Mediterranean diet.^{19,35,38,39} Oleic acid, the main mono-unsaturated fatty acid found in olive oil, has been hypothesized to regulate key cancer-related oncogenes by repressing their translation. Specifically, oleic acid has been found to suppress a well-characterized oncogene (*neu* or *erb-2*) that plays a key role in the aetiology, progression and chemosensitivity of various types of human cancer including breast, ovarian and stomach carcinomas.^{64,65} The antitumour properties proposed above have been related not only to its content in oleic acid, but also due to its richness in antioxidant components which are scavengers of reactive species.⁶⁶⁻⁶⁸ While olive oil is a rich source of oleic acid and polyphenolic compounds, it is the fruit content of the Mediterranean diet that provides the high daily intake of alpha-carotene, beta-carotene and beta-cryptoxanthin.⁶⁹ Epidemiological studies have indicated a statistically significant inverse relationship between these antioxidant carotenoids and lung cancer even after adjusting for smoking, indicating the potential role of fruit and vegetable intake of the Mediterranean diet on the incidence of lung cancer among populations that adhere to this diet.^{70,71} Consistent with inhibition of lung cancer cell growth, beta-cryptoxanthin (found in abundance in citrus fruits) has been found to inhibit the growth of A549 cells, a non-small-cell lung cancer cell line, in a dose-dependent manner and induce the mRNA levels of retinoic acid receptor beta in BEAS-2B cells, which suggests an antiproliferative mechanism.⁷² Elevated dietary intake of fruits, vegetables and wild edible greens also provides higher amounts of carotenoid, L-ascorbic acid, phyloquinone, gamma-tocopherol, alpha-tocopherol and total polyphenols.³⁹⁻⁴⁶ Alpha-tocopherol and gamma-tocopherol are two of the major chemical forms of vitamin E. Like other antioxidants, vitamin E can scavenge free radicals and may, as a result, prevent oxidative tissue damage by trapping organic free radicals. By including large quantities of fresh greens in their diet, populations that adhere to the Mediterranean diet guarantee a substantial daily intake of these valuable antioxidants, many of which have been shown to be associated with a lower risk of cancer.⁴⁶ However, because both dietary habits and balanced meals are associated through a complex interaction between nutrients and food items, the investigation of the interrelation between aspects of diet and carcinogenesis has proved to be extremely difficult. Limitations exist when considering specific food items or even one or two nutrients as the only risks for the incidence of cancer or even

as playing a role in cancer prevention. This is not only due to the complexity of dietary habits and meals and their carcinogenic effects, but can also be due to the fact that human bodies have, or potentially have, an innate ability to adapt flexibly to certain variations in diet and meals to maintain overall homeostasis.

Active/passive smoking, the Mediterranean diet and respiratory disease

Asthma

Oxidative stress has been widely recognized as an important component of airway inflammation in asthma. Exposed to the oxidative particles of tobacco smoke and/or other oxidative-toxic components, many reactive oxygen species can be created which, in turn, deplete glutathione buffers and lead to a destabilized situation in epithelial cells. Glutathione is an abundant airway antioxidant that reduces organic hydroperoxides and protects the airway from lipid peroxidation.^{73,74} Such an oxidative substance is peroxynitrate, which has been shown to cause oxidative stress in epithelial cells and has been indicated to play a role in the molecular and cellular response to air pollution.^{74,75} Indeed, children with severe asthma have increased biomarkers of antioxidant stress in the epithelial lining fluid of their airways, which are associated with a shift in the glutathione redox potential towards the more oxidized state. Interventions to increase epithelial lining fluid glutathione concentrations have been suggested as a therapeutic intervention.⁷⁶

The Mediterranean diet is characterized by a large intake of fresh fruit, vegetables, wild greens and olive oil, in which antioxidants, such as glutathione, can be found in substantial quantities and could indicate a protective effect.^{39,46} It is this exact dynamic equilibrium between oxidative and anti-oxidative substances that is where the interaction between nutritional and environmental exposures takes place.^{77,78} Despite the above scientific indications, there is limited evidence of the effect of separate antioxidant supplementation on glutathione levels and the outcome of asthma, when providing additional selenium, magnesium and vitamin C, in the context of randomized control trials.⁷⁷ It is possible that the separate antioxidants have a less significant role on their own than when they are provided within the context of the Mediterranean diet, most possibly due to synergistic interactions with other dietary compounds such as lipids. Indeed, the optimal balance between dietary alpha-linolenic acid and linoleic acid, such as in the traditional diet of Crete, has recently been shown to reduce the risk for asthma.⁷⁹ Adherence to the Mediterranean diet, but not antioxidant supplementation, has a protective effect against asthma and other illnesses that has been strongly correlated with active and passive smoking.^{5,80} Epidemiological evidence has indicated that children who adhere to the Mediterranean diet are less likely to develop asthma, wheezing, sneezing and allergies.^{81,82} In addition to modifying children's reactions to SHS, high adherence to the traditional Mediterranean diet has been found to increase the likelihood of asthma being under control

in adults, indicating an additional public health implication of adherence to a Mediterranean-style diet.⁸³

Chronic obstructive pulmonary disease

Chronic obstructive pulmonary disease (COPD) is associated with a high incidence of morbidity and mortality, and both active and passive smoking can cause COPD exacerbation and progression.⁸⁴ As with asthma, COPD can also be influenced through an imbalance in antioxidants, especially among smokers whose circulating neutrophils (in both blood and alveoli) produce more oxidative molecules and lead to bronchial hyper-responsiveness, suggesting a pathogenetic pathway between oxidative stress and airway abnormalities in COPD.^{85–88} Numerous studies have investigated the relationship between antioxidants, pulmonary function and COPD.⁸⁸ Data from the NHANES III indicated that serum antioxidants vitamin C, vitamin E, selenium and beta-carotene are associated with lung function, while the Dutch MORGEN study revealed that higher intake of vitamin C and beta-carotene was also correlated with a higher forced expiratory volume in 1 second, a significant prognostic indicator of COPD.^{89,90} Epidemiological studies, such as that by Walda et al., have also confirmed the relationship between dietary intake and 20-year COPD mortality in middle-aged men.⁹¹ In this prospective cohort study of 2917 men, the authors observed an inverse trend of 20-year COPD mortality with an increase in dietary intake of fruit and vitamin E, intake of which would be substantial in populations that adhere to the Mediterranean diet. Moreover, it has been hypothesized that it is the antioxidant and anti-inflammatory properties of the dietary polyphenols and flavonoids that might explain these beneficial effects of adherence to such a diet.^{92–94}

Conclusions and public health implications

While the evidence on the role of antioxidants and dietary intake on cancer, cardiovascular, respiratory and other chronic diseases is extensive, knowledge of the role of antioxidant or micronutrient supplementation on these outcomes is incomplete and contradictory as the evidence is insufficient to conclude that micronutrient supplementation has a definite protective effect.^{95–99} To date, the existing scientific literature indicates that the dietary intake of beneficial antioxidants, lipids and other micronutrients, through adherence to the Mediterranean diet, can have a protective effect on cancer, cardiovascular and respiratory diseases, and it is possible that this diet can act as a positive effect modifier of the role of active and passive smoking on health.

Therefore, at a personal level, a balance-focused dietary habit is essential for promoting personal health,¹⁰⁰ and this should be accompanied by the avoidance of exposure to SHS and/or smoking cessation. From a policy and scientific point of view, as an essential and immediate challenge for the future, a large amount of effort needs to be put into developing the methodology and dietary/living protocols to achieve an ideal, healthy lifestyle that can be promoted at a population-based level.

Although the best ways to avoid the negative health ramifications of active and passive smoking are to stop smoking and minimize exposure to SHS, adherence to the Mediterranean diet could provide an additional supportive effect and thus have significant implications on clinical outcomes and public health.

Ethical approval

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Competing interests

None declared.

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