

Chemoprotective Properties of the Mediterranean Diet for Skin Cancer

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Abstract

The Mediterranean diet (MD) has proven itself protective against many diseases, including cancer. A Mediterranean diet comprises whole grains, vegetables, fruits, fish, extra virgin olive oil, red wine, and legumes. Foods studied within this diet contain high levels of antioxidants and anti-inflammatory compounds. The diversity of healthy foods and numerous nutritional benefits maximizes chemoprotection with a variety of protective substances. The Mediterranean diet has high concentrations of polyphenols and offers chemoprotective properties including carotenoids, vitamins, and flavonoids. These phytochemicals contain antioxidant properties that prevent DNA damage. High levels of omega-3 within this diet have been studied to slow down cancer development, cancer cell proliferation, angiogenesis, survival, inflammation, and metastasis. The consumption of extra virgin olive oil has been found to lower the incidence of dermatological diseases. Wine-making byproducts inhibit the growth of A431 skin cancer cells and induce cytotoxicity and apoptosis only to cells with morphological changes. Our review addresses the chemoprotective properties of how a Mediterranean diet pertains specifically to skin cancer. The Mediterranean diet has many beneficial effects on dermatological health and chemoprotection against skin cancer. The impact of chemoprotection from a Mediterranean diet allows for development of a nutritional approach to minimize skin cancer incidence and skin cancer metastasis via dietary changes.

Keywords: mediterranean diet; skin cancer; healthy foods; morphological changes

Introduction

Diet and nutrition play an important role in overall health and cancer prevention. Certain diets are suggested to influence the onset and course of cancer more than others, specifically the Mediterranean diet (MD). In the study of skin cancer, diet has been found to have a direct influence in regard to evidence continuing to emerge on the positive effects of the Mediterranean diet on skin cancer incidence rates. As contemporary research unfolds, it underscores the profound influence of dietary patterns like the Mediterranean diet on skin cancer prevalence, attributing this to the nuanced interplay of nutrients and their synergistic interactions. The development of skin cancer and mutations leading to DNA damage is primarily caused by exposure to ultraviolet (UV) rays from the sun. UV exposure causes damage to the skin by generating free radicals which produce inflammation and damage cellular function and DNA. As DNA damage continues to accumulate, changes in an individual's genes can occur, leading to skin cancer. Research shows diets, such as the Mediterranean diet, that are high in antioxidants, vitamins, and nutrients, help fight off free radicals and prevent the DNA damage contributing to skin

cancer. UV exposure's effect on skin cancer has been studied and found to cause damage at least partly by depleting antioxidants within the body. Replacing antioxidants with a nutritious diet is imperative to bolstering the body's weakened immune defenses after UV exposure.

Poor diet correlates with higher cancer rates, including higher skin cancer rates. While diets will not protect from specific drivers of disease states or exposure to sun, it can have a positive impact on other facets of health or lifestyle factors that contribute to cancer. Research has shown diets rich in antioxidants and omega-3 fatty acids help protect from skin cancer [1]. Foods including olive oil, yogurt, fish, and a wide variety of fruits and vegetables assist with fighting the oxidizing effects of the sun. In addition to sun protection, following a Mediterranean diet also has a highly suggested benefit on the development of skin cancer, including melanoma and nonmelanoma skin cancers. Similarly, vitamins C, E, and A, zinc, carotenoids, selenium, lycopene, and polyphenols found in Mediterranean-rich diets have been studied to help prevent skin cancer. In essence, the Mediterranean diet is a cornucopia of health, proffering an array of nutrients pivotal for holistic skin cancer prevention.

Discussion

The Mediterranean diet is based in the rich culture of the region; it consists of many foods and contains a wide variety of nutritious compounds. This dietary pattern is based on a high intake of olive oil, fresh fruit, legumes, nuts, and vegetables, a moderate intake of fish, dairy products, ethanol (in the form of red wine), and a low consumption of red meats with overall moderate quantities of processed foods [2,3,4,5]. Herbs such as sage, basil, oregano, and rosemary are also incorporated into the foods of the Mediterranean diet for further flavoring and nutrients [3]. These aspects of the Mediterranean diet make it unique in today's food culture, where many foods are highly processed and a high intake of fruits and vegetables is not commonplace. The Mediterranean diet has proved to be a well-varied diet with many nutritional benefits and may increase overall health and longevity [6]. Many of these foods are rich in antioxidants, a diet which may protect against the free radicals produced when exposed to UV radiation, and thus aid in the prevention of skin cancer [6]. Specifically in this discussion, studies will be discussed on the use of the Mediterranean diet in the prevention of skin cancer and specific compounds will be evaluated in terms of their effectiveness and protective properties.

A hospital-based case-control study by Fortes, et al. in Rome, Italy evaluated the protective role of the Mediterranean diet for cutaneous melanoma through a food frequency questionnaire (FFQ) and a skin examination, with significant findings [7]. There were protective effects of vegetable consumption five or more times a week (especially for cruciferous, leafy green, carrots), fruit consumption once or more a day (especially for citrus fruits), fresh herbs (especially for rosemary), nuts, omega-3 fatty acid rich fish, fish, shellfish, and tea [3, 4, 7]. Rosemary is rich in carnosol, an inflammatory compound that blocks protein kinase C signaling and reduces proinflammatory leukotrienes [3]. In this study, tomatoes had no association with a decreased risk of melanoma, while foods such as meat, dairy, eggs, and liver had no association with an increased risk of melanoma [7]. These findings are consistent with the literature that foods found in the Mediterranean diet are protective for the development of melanoma. Limitations of this study are present with recall bias of food frequency questionnaires (FFQs), the concentration of Caucasian subjects, and the hospital-based population. While there are many factors that

go into the development of melanoma, this study provides clear data for the protective effects of the Mediterranean diet to further propose the beneficial effects this dietary pattern can play in the prevention of skin cancer.

In a large prospective cohort study of French women, Mahamat-Saleh, et al. evaluated the role of the Mediterranean diet via questionnaires of reported skin cancer events and a food questionnaire scored to adherence of a Mediterranean diet. This study found a significant decrease in skin cancer for participants who had a high score of adherences to the Mediterranean diet and an inverse and linearly associated score of the Mediterranean diet to the risk of melanoma and basal cell carcinoma (BCC) [6]. When evaluating single dietary items within the Mediterranean diet, there was a decreased risk of skin cancer with increased intake of vegetables [6]. Sources of monounsaturated fat in the typical Mediterranean diet are largely olive oil, while in France the main source of this compound is from poultry and pork and the scoring was adjusted accordingly [6]. This can be extrapolated to mean that the compound consumed, even from a different source than is typically included in the Mediterranean diet, can still be beneficial and play a protective role in the development of skin cancer. Both studies discussed the role that vegetables have in chemoprotection. Fruits and vegetables are part of a well-balanced diet, containing many nutritious compounds such as vitamins, dietary fiber, flavonoids, folates, and polyphenols that are not found in high sources elsewhere, lending to their anti-tumorigenic effects for epithelial cancer [2, 4]. Citrus fruits are rich in Vitamin C which promotes the formation of collagen and triterpene compounds that protect against skin cancer [4]. Dietary polyphenols have been discussed as one of the "most promising" compounds in the prevention of skin cancer [8]. Fruits and vegetables are known to be part of a balanced diet, which can be seen through guidelines such as MyPlate and the former Food Pyramid. These studies further emphasize the role fruits and vegetables have in a nutritious diet.

Lipids

Omega-3 polyunsaturated fatty acids (PUFA) are essential fatty acids found in abundance in the Mediterranean diet in both animal and plant sources and are typically associated with their anti-inflammatory effects. Fatty fish (such as sardines and mackerel) and nuts (such as almonds and walnuts) are rich sources of this nutrient; they reduce

inflammation within the body and slow the progression of cancer [2, 5, 6]. UV damage to the skin is in part through immune suppression. A randomized controlled trial by Pilkington et al. confirmed the protective effects that omega-3 PUFAs have on photo-immunosuppression to further confirm the role this nutrient has in the protective effects of developing skin cancer [9]. However, many modern Western diets are lacking in this essential fatty acid and are instead diets rich in inflammatory compounds, such as omega-6 PUFAs.

Omega-6 is an essential PUFA found in abundance in Western diets and has been shown to reduce the risk of skin cancer with limited consumption and increase the risk of skin cancer when consumed in abundance, which is possibly through its metabolism into PGE2 (a tumor promoter) through the cyclooxygenase pathway [9,10]. PGE2 has been implicated in BCC and squamous cell carcinoma (SCC) [10]. While both omega-3 and omega-6 PUFAs are necessary for proper metabolic function and are both part of a well-balanced diet, consuming a diet with an optimized ratio of omega-6 to omega-3 PUFAs is ideal. It has been suggested that the ratio of omega-6 to omega-3 PUFAs in Western diets is around 15:1, which leads to many chronic diseases [11]. In contrast, humans evolved with a ratio of omega-6 to omega-3 of 1:1 to 2:1 [11]. The optimal ratio is essential because human cells lack the ability to convert omega-6 into omega-3 [11]. There is a vast difference between the historic human diet to the Western diet consumed in the present day. Lowering this ratio to include more favorable omega-3 PUFAs can not only help protect against skin cancer but many other inflammatory conditions, such as heart disease. Optimal ratios have been evaluated for some chronic diseases such as asthma and rheumatoid arthritis, but the optimal ratio of these PUFAs for the prevention of skin cancer still remains to be evaluated.

Olive oil is rich in phenolic compounds including polyphenols, secoiridoids, lignans, and squalenes which are rich antioxidants and have been shown to protect against cancer [2,12]. These antioxidant properties play a role in decreasing inflammatory processes and are associated with a lower risk of chronic diseases such as diabetes, cancer, skin disease, and heart disease [5]. Olive oil is a cornerstone in the Mediterranean diet. It is estimated that the average yearly intake of olive oil in the region ranges from a few kilograms per person in countries such as France to fifteen kilograms per person in Greece (where olive

oil is the main monounsaturated food source); in areas with higher intake of olive oil there is a lower incidence of cancer [6,12]. Olive oil is 70% of the lipid source in the Mediterranean diet [5].

Squalene, which can be found in olive oil, is thought to play a role in the prevention of skin cancer, because it is largely transferred to the skin where it is found in large amounts in sebum [12,13]. In an *in vitro* and *in vivo* study by Ekanayake Mudiyansele et al., the chemoprotective properties of human sebum were evaluated after irradiation with UVA and UVB. It was found that squalene was depleted when exposed to UVA and photo-oxidation products were produced and there was an increased amount of squalene isomers, which may be a photo-oxidative stress marker [13]. However, further studies are needed to define the specific role squalene has in the prevention of skin cancer.

There are many varieties of olive oils on the market. The highest quality of olive oil is extra-virgin olive oil (EVOO), which is olive oil that has been bottled after the first processing [12]. In comparison, refined virgin olive oil (RVO) is further processed from EVOO and has lower levels of some phenolic compounds, especially lignans [12]. The waste produced from the production of olive oil is higher in antioxidants than in olive oil itself in the form of flavonoids, polyphenols, anthocyanins, and tannins which can be found in the olive leaves, seeds, and wastewater post-oil production [5]. In comparison, seed oils, which are found in abundance in modern Western diets, have almost none of this phenolic compound and squalene [12]. Based on fats alone, it is evident that the Mediterranean diet supplies nutrients needed to protect against chronic disease and cancer.

Wine and Wine-making byproducts

Grapes are rich in many phytochemicals. Wine is consumed in moderate amounts as part of the Mediterranean diet and contains many of the polyphenols and antioxidants once found in the grapes [2,4]. White wine has less phytochemicals than red wine; in comparison spirits consumed in other countries and dietary patterns have next to no phytochemicals [4]. Phytochemicals in wine and grapes include resveratrol, tannins, anthocyanins, and catechins [4]. While consumed in moderation, the wine as part of the Mediterranean diet may confer protective benefits towards health and skin cancer prevention through these phytochemicals.

Production of wine can generate a large amount of waste; it is estimated that a quarter of what is

produced in wine production is waste product, resulting in 20 million tons of waste each year [5,14]. This waste consists of grape pomace, grape skins, grape pomace, grape pulp, seeds, stalk, and wine lees [5,14]. These waste products still retain many of their antioxidant and anti-inflammatory properties that the grapes once maintained and have demonstrated utility for the prevention of cancer [5]. Instead of wasting these useful compounds, it is imperative to evaluate them for nutritional benefits to possibly integrate them into the diet. It has been suggested that enriching foods with these compounds could produce functional foods to help combat disease while lessening the waste burden that wine making can place on the environment [14]. With a constantly changing food environment utilizing nutrients that are readily available is an effective way to promote nutritional choices.

Skin cancer may also benefit from these wine-making byproducts. Specifically, the polyphenol resveratrol found in grapes and wine has been shown to play a role in skin cancer [5]. An *in vitro* study by Grace Nirmala, et al. evaluated the role of grape peel and seed extracts by incubating A431 cells (human epidermoid carcinoma) with these compounds and found significant apoptosis and necrotic cells when compared to the control via the production of reactive oxygen species and induced cytotoxicity [5,15]. Limitations of this study are that this was an *in vitro* study; however, it shows a promising use for wine-making byproducts in the prevention of skin cancer and necessitates further studies to be carried out to specifically evaluate the use of these compounds as a dietary supplement.

The Mediterranean diet may be a beneficial way to reduce the incidence of skin cancer, while promoting a nutritious and well-balanced diet and lifestyle. However, the mainstay of skin cancer prevention is to avoid the sun's ultraviolet (UV) rays during the peak hours during the day, avoid tanning beds, and wear sun protective clothing or sunscreen while in the sun. The Mediterranean diet may be used as an adjunctive to sun protective measures to further protect in the development of skin cancer.

Areas for Future Research

The beneficial implications of the Mediterranean diet (MD) for overall health and its potential chemoprotective properties against skin cancer have been elucidated. However, there are several areas within the Mediterranean diet that warrant further exploration. Firstly, while the Mediterranean diet's

constituents, like olive oil and omega-3, have shown individual benefits, a comprehensive understanding of their combined effect and potential synergistic roles is needed. Quantifying the optimal ratio of omega-3 to omega-6 PUFAs for maximal chemoprotection could be pivotal. Additionally, while wine-making byproducts have shown potential in preliminary studies, their exact role, dosage, and application in skin cancer prevention remain largely uncharted. The challenge of effectively integrating these byproducts into everyday diets, without optimal effects, presents another research opportunity. Moreover, the effectiveness of the Mediterranean diet when combined with traditional sun protection measures and its potential in reducing pre-existing skin cancer risks needs to be further elucidated. Furthermore, while current studies predominantly involve *in vitro* tests, there remains a pressing need for comprehensive *in vivo* trials, population-based cohort studies, and clinical evaluations to validate findings and ensure they are translatable to real-world scenarios.

Conclusion

Foods studied within the Mediterranean diet are found to be protective against skin cancer with high levels of nutrients, vitamins, protein, omega-3 fatty acids, antioxidants, and anti-inflammatory compounds. The diversity of healthy foods and numerous nutritional benefits maximizes chemoprotection with a variety of protective substances. Previous research studies have found phytochemicals in the Mediterranean diet contain antioxidant properties that prevent DNA damage, extra virgin olive oil lowers the incidence of dermatological diseases, and omega-3 fatty acids slow down cancer development, cancer cell proliferation, angiogenesis, survival, inflammation, and metastasis. This review addresses the chemoprotective properties of how a Mediterranean diet pertains specifically to skin cancer and the need for additional research with larger clinical trials to show the significance of the impact of certain nutritive substances and the interaction between specific nutrients on cancer prevention. The impact of chemoprotection from a Mediterranean diet continues to show significance through recent research studies and suggests development of a nutritional approach as a substantial lifestyle change to minimize skin cancer.

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