Lithuanian University of Health Sciences, Kaunas, Lithuania

Department of Dermatology

Author: Husein Omari

Supervisor: prof. Skaidra Valiukevičienė

Risk of cutaneous malignant melanoma (CMM) in relation to diet

Lithuanian University of Health Sciences (LSMU), Kaunas, June 2018
ACKNOWLEDGMENT

I would first like to thank my thesis supervisor whom office door was always open for any kind of help, Professor Skaidra Valiukevičienė the head of the Dermatology department at Kaunas Medical University- Lithuania.

Special thanks to Doctor Silvija Kontautiene from the Dermatology department at Kaunas Medical University in Lithuania for helping and advising me at the beginning of my thesis work.

I would also like to thank the one who answered my questions at times when things were unclear, Doctor Samuel Attias, a research expert at Bnei Zion medical center- Haifa- Israel.

And at last, thanks to the one who helped me find articles online, Ilana Merhav- the head librarian at Bnei Zion medical center, Haifa- Israel.

Thank you all for making this possible.
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>SECTION</th>
<th>PAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Title page</td>
<td>1</td>
</tr>
<tr>
<td>Acknowledgments</td>
<td>2</td>
</tr>
<tr>
<td>Table of contents</td>
<td>3</td>
</tr>
<tr>
<td>Abstract</td>
<td>4-5</td>
</tr>
<tr>
<td>Keywords</td>
<td>4-5</td>
</tr>
<tr>
<td>Introduction</td>
<td>6-9</td>
</tr>
<tr>
<td>Aim and objectives</td>
<td>10</td>
</tr>
<tr>
<td>Materials and methods</td>
<td>11-12</td>
</tr>
<tr>
<td>Results</td>
<td>13-21</td>
</tr>
<tr>
<td>Discussion</td>
<td>22</td>
</tr>
<tr>
<td>Conclusions</td>
<td>23-24</td>
</tr>
<tr>
<td>Conflicts of interest</td>
<td>25</td>
</tr>
<tr>
<td>References</td>
<td>26-30</td>
</tr>
</tbody>
</table>
Risk of cutaneous malignant melanoma (CMM) in relation to diet: A systematic review

Husein Omari, medical student VI

ABSTRACT

Aim and objectives:
It is well known that sun exposure together with genetic factors are the main risk factors for melanoma development. Several studies in recent decades have brought the sight on the importance of our diet in the progression or prevention of cutaneous malignant melanoma (CMM), which is the most common form of skin cancer (98% of cases). This study is aimed to focus on the available data centered on the topic, to summarize them, and make a valid conclusion.

Study design:
A systemic review of previous observational studies which assessed the relation between dietary habits and CMM.

Materials and methods:
The electronic databases “NCBI”, “Medscape”, “Sciencedirect”, and “Pubmed” were used to find articles. The quality of the articles were evaluated by reading and re-reading them carefully. Various official medical books were also used to gather different information during my research work.

Results:
42 articles were selected. 15 articles were excluded for not fulfilling the criteria, while the other 27 articles fulfilled the inclusion criteria. 3 articles about coffee, 2 about green tea, 2 about plants, 6 about vitamins (A, D, C, and E), 2 about unsaturated fatty acids, and 1 about Omega-3 obtained from fish showed protective roles against CMM.
1 article about coffee consumption, 1 about alcohol, 2 about plants, 1 about saturated fatty acids, 3 about sugar and 2 about red meat showed increased risk of CMM.

Conclusions:
A tendency of reduction of CMM is associated with higher fish, polyunsaturated fats, vegetables, fruits, coffee, tea, and vitamins intake. While an increased risk of CMM with the consumption of alcohol, saturated fats, and sugar in high amounts.

Keywords:
-Melanoma
-CMM
-Diet
Piktybinės odos melanomos (OM) rizika, susijusi su mityba: sisteminė literatūros apžvalga

Husein Omari, medicinos studentas VI

SANTRAUKA

Raktiniai žodžiai:
- Odos melanoma
- Dieta

Tikslas uždaviniai:
Gerais žinomą, kad ultravioletiniai spinduliai kartu su genetiniais veiksniais yra pagrindiniai melanomos vystymosi rizikos veiksniai. Pastarųjų dešimtmečių moksliniai tyrimai rodo reikšmingą ryšį tar dietos ir piktybinį odos navikų progresavimo ar jų profilaktikos. Šio tyrimo tikslas – išanalizuoti pasirinkta tema mokslinės literatūros duomenis, apibendrinti juos ir pateikti išvadas.

Studijos dizainas:
Sisteminė ankstesnių mokslinių tyrimų apžvalga, kurioje įvertinta mitybos įpročių ir piktybinės odos melanomos (OM) ryšys.

Medžiagos ir metodai:
Straipsnių paieškai naudota elektroninės duomenų bazės. Straipsnių kokybė buvo įvertinta atidžiai ir jie visi perskaityti. Darbe susijusia tema panaudotos ir medicinos knygos.

Rezultatai:
42 straipsniai buvo atrinkti. 15 straipsniuose nerasta absoliuatoriaus ryšio tarp dietos kaip rizikos veiksnio OM, o kiti 27 straipsniai parodė, kad žuvų, daržovių, vaisių, kavos, arbatos, vitaminų A, C, D ir E apsauginis vaidmuo yra įrodytas. Kiti straipsniai, kuriuose kalbama apie alkoholį, riebalus ir cukrų dietoje, turėjo žalingą poveikį, dėl kurio padidėja rizika vystytis OM.

Išvados:
Nustatyta tendencija mažėti OM rizikos mažinimas naudojant didesnę žuvų, daržovių, vaisių, kavos, arbatos ir vitaminų kiekį. Nors padidėjusi OM rizika vartojant alkoholį ir riebalų bei cukraus suvartojimą dideliais kiekiais.
1. Introduction

Melanoma is an aggressive skin cancer with a high potency to spread to other sites and organs. It is considered to be among the most common findings during skin physical exam. Atypical moles, also known as dysplastic nevi, are usually benign, but may resemble melanoma, and people who have them are at increased risk of developing melanoma [1]. The disease develops when unrepaired DNA damage trigger mutations that lead the skin cells to multiply rapidly and form a malignant mass [2].

In western countries, melanoma is rapidly increasing in incidence. During the past 60 years there have been 17 folds and 9 folds increase in incidence of melanoma for men and women, respectively. In the same 6 decades there has been tripling mortality rate for men and doubling for women [4].

It is thought that there will be more than 91,000 new cases of melanoma and an estimated 10,000 deaths in the United States by the end of 2018 [3].

Putting a light on the anatomy, the epidermis part of the skin consists of 3 layers: squamous cells, basal cells, and melanocytes. Melanoma develops in the melanocytes layer which consists of pigment-producing cells originate from the neural crest and then migrate to the skin, the meninges, mucous membranes, upper esophagus, and the eyes [4].

It can develop anywhere on the body, with the main initial development sites for men are the chest and the back, for women the legs. The face and neck are also common places where cancerous moles can be seen [7].

There are 4 main form of melanoma. Superficial cutaneous melanoma is the most common form and is predominantly a malignant disease (70-80% of cases) [5], while the rest of melanoma forms are Nodular melanoma, Lentigo maligna melanoma, and Acral lentiginous melanoma [6].

The disease is much more prevalent in brighter skinned population (98%) than dark skinned, but the prognosis is worst for dark skinned patients because the disease is usually diagnosed in more advanced stages due to the fact that it is harder to detect skin changes during skin physical exam for such patients [8].
The main risk factors of cutaneous malignant melanoma (CMM) include advanced age, light skin, intense sun exposure with increased tendency to burn (especially during childhood period), immunosuppressive diseases, genetic factors such as familial atypical mole and melanoma (FAM-M syndrome) [9], as well as risks related to the presence of CDKN2A, BRAF, MC1R, and p53 gene mutations [10].

It is believed that the lack of education and knowledge about the prophylactic measures (UV light protection for example) which are needed to be taken in order to reduce prevalence or prevent the development of melanoma, is the main problem that faces medicine in the fight against the most life threatening, deadly disease in dermatology. Socioeconomic factors, beside education, knowledge, and prophylactic measures, could play a part in the development of CMM in certain groups of people [13].

In order to assess CMM dermatologists usually look at the warning signs, or the appearance of skin changes during the physical exam, which are also called the ABCDEs of melanoma [14]. The ABCDEs of melanoma are well summarized in (Table.1.1) [15].

Tab.1. The ABCDEs of CMM [15].
Journal of the American Academy of Dermatology.

<table>
<thead>
<tr>
<th>A</th>
<th>Asymmetry- One half unlike the other half.</th>
</tr>
</thead>
<tbody>
<tr>
<td>B</td>
<td>Border- An irregular, scalloped, or poorly defined border of the mole.</td>
</tr>
<tr>
<td>C</td>
<td>Color- Varied color from one area to the other. Moles have shades of tan, brown, or black. Sometimes white, red, or blue.</td>
</tr>
<tr>
<td>D</td>
<td>Diameter- Melanomas are usually &gt; 6mm when diagnosed. But they may be of any size.</td>
</tr>
<tr>
<td>E</td>
<td>Evolving- A mole or skin lesion that looks different than the rest in size, shape, or color.</td>
</tr>
</tbody>
</table>

*The ABCDE is used by dermatologists as a warning signs at time of the physical assessment of patients. The presence of 1 sign or more on the skin is a call for further investigation. The (E) - Evolving has become the most important factor in diagnosing Melanoma [15].

Once a CMM is diagnosed, it is staged according to the TNM system, where T- stands for tumor. N- for lymph nodes. And M- for metastasis of the tumor [16]. The TNM classification and staging system for cancer is provided according to The American Joint Committee on Cancer (AJCC) in table 2 (Tab.2)
Tab. 2. **The TNM classification for CMM** [16].
The American Joint Committee on Cancer (AJCC) tumor/node/metastasis (TNM) classification and staging system for cancer.

<table>
<thead>
<tr>
<th>TX</th>
<th>NX</th>
<th>M0</th>
<th>M1a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary tumor cannot be assessed (i.e. curettage of melanoma)</td>
<td>Regional nodes cannot be assessed</td>
<td>No detectable evidence of distant metastases</td>
<td>Metastases to skin, soft tissue (including muscle), and/or non-regional lymph nodes</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>T0</th>
<th>N0</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>No evidence of primary tumor. Tumors are in situ. Meaning they did not penetrate below outer skin layer.</td>
<td>No regional metastases detected</td>
<td>M1a</td>
<td>Lung metastasis, with or without M1a involvement</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Tis</th>
<th>N1 - One tumor-node</th>
<th>N1a</th>
<th>N1b</th>
<th>N1c</th>
<th>M1b</th>
<th>N2a</th>
<th>N2b</th>
<th>N2c</th>
<th>M1c</th>
<th>N3a</th>
<th>N3b</th>
<th>N3c</th>
<th>M1d</th>
<th>N4a</th>
<th>N4b</th>
<th>M1e</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melanoma in situ</td>
<td>N1 - One tumor-node</td>
<td>N1a</td>
<td>N1b</td>
<td>N1c</td>
<td>M1b</td>
<td>N2a</td>
<td>N2b</td>
<td>N2c</td>
<td>M1c</td>
<td>N3a</td>
<td>N3b</td>
<td>N3c</td>
<td>M1d</td>
<td>N4a</td>
<td>N4b</td>
<td>M1e</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>T1-Thickness ≤1.0 mm.</th>
<th>T1a: &lt;0.8 mm without ulceration</th>
<th>N1a</th>
<th>N1b</th>
<th>N1c</th>
<th>M1b</th>
<th>N2a</th>
<th>N2b</th>
<th>N2c</th>
<th>M1c</th>
<th>N3a</th>
<th>N3b</th>
<th>N3c</th>
<th>M1d</th>
<th>N4a</th>
<th>N4b</th>
<th>M1e</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>T1b: &lt;0.8 mm with ulceration, or 0.8-1.0 mm with or without ulceration</td>
<td>N2a</td>
<td>N2b</td>
<td>N2c</td>
<td>M1c</td>
<td>N3a</td>
<td>N3b</td>
<td>N3c</td>
<td>M1d</td>
<td>N4a</td>
<td>N4b</td>
<td>M1e</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>T2-Thickness &gt;1.0-2.0 mm.</th>
<th>T2a: Without ulceration</th>
<th>N3a</th>
<th>N3b</th>
<th>N3c</th>
<th>M1d</th>
<th>N4a</th>
<th>N4b</th>
<th>M1e</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>T2b: With ulceration</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>T3-Thickness &gt;2.0-4.0 mm. with metastasis</th>
<th>T3a: Without ulceration</th>
<th>N4a</th>
<th>N4b</th>
<th>M1f</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>T3b: With ulceration</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>T4-Thickness &gt;4.0 mm. with metastasis</th>
<th>T4a: Without ulceration</th>
<th>N4a</th>
<th>N4b</th>
<th>M1f</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>T4b: With ulceration</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Over the past several decades melanoma incidence have been rising rapidly in both developing and developed countries [52]. Several previous studies reported a link between obesity, which is reflected by our BMI value, and CMM [53]. Other studies reported a close relationship between dietary habits and CMM incidence.

The role of diet in defining our health is a subject that has been always needed to be discussed in order to educate people around the world to consume healthier food; “You are what you eat”, is a sentence each one of us have heard at a point during our life. In some respect, our diet identifies our approach to life, our ethnicity, religion, or maybe both. “I love meat”, “I am a vegetarian”, “I am Italian and I love pasta”, “I eat fish every Friday”, “I am American and I eat a lot of hot dogs and hamburgers”, “I am Turkish and I love sweets”. The list of such phrases can go on and on to reflect how different parts of this world are exposed to different dietary habits [17].

The World Health Organization (WHO) and the American Cancer Society (ACS) recommend cancer patients to consume a plant-based diet more often and to participate in a 150 minutes of moderate intensity exercise per week [18]. A good lifestyle with healthy dietary habits are thought to be protective factors for melanoma, and all forms of cancer in general [11]. Studies have shown that 30-40% of cancers can be prevented by lifestyle modification and dietary measures alone [12].

The first thought about dietary habits and the risk they expose on cancer prevalence started back in the early 1800s, if not before [19]. In 1975, under the leadership of Ernst Wynder, the American Health Foundation together with the National Cancer Institute, held the conference “the 1975 Key Biscayne” on diet and the risk of cancer. At this conference, and for the first time, researchers from around the world could discuss epidemiological, preclinical, and molecular studies associating nutrition and cancer prevention [20].

This hypothesis has recently become a very popular subject to investigate. An increasing number of studies have examined the risk of food we intake on a daily basis and the prevention of cancer. Since the early 1990s, experts of dermatology have tried to prove the use of nutritional supplements as an adjuvant therapy in order to protect our skin from various skin diseases, and especially the protection from the harmful effects of UV light, such as skin oxidation and carcinogenesis [21]. Oxidation is a process involved in many skin disorders, it has a negative biological effect on our organs by generating reactive oxygen species (ROS) and free radicals that in turn promote carcinogenesis. Taking that in consideration we may think that nutritional sources with antioxidant activities may have a protective role against the UV adverse effects on the skin, thus, have a possible preventive effect against skin cancer [22].

It is important to note that nearly 70% of all anticancer drugs were made using natural sources. Thus, diet plays an important role in the treatment of cancer in general, and in our interest, melanoma in particular [23].
2. **Aim and objectives**

The main goal of this study was to clarify the association between diet and CMM by collecting available evidences using databases from the internet, to read them carefully, and to summarize results by writing a systematic review of published articles in the past 15 years.

Trying to collect data about several kinds of food and their relation to CMM, and the big variation of dietary habits collected during the search forced the results section of the article to be divided into several parts. Each part contained a specific type of diet (i.e. Coffee, Alcohol, Fats, Vitamins, etc.).
3. **Materials and methods**

The electronic databases “NCBI”, “Medscape”, “Sciencedirect”, and “Pubmed” were used for the search using the keywords “melanoma” and “diet”. The articles were found relevant if they were in English language, and were written between the years 2003-2018.

The inclusion criteria that were taken in caution while searching for articles were as following:
- Articles in English.
- Articles written between the years 2003-2018.
- Articles relate to melanoma skin cancer and diet.
- The study design: Case study and reports, Randomized clinical trials (RCT), or Retrospective studies.
- The study population: examining dietary factor in human, *in-vitro*, or using lab animals such as mice.

The exclusion criteria were as following:
- Articles written in non-English languages.
- Articles written before the year 2003.
- Articles related to the relation between non-melanoma skin cancer and diet.

The abstract, introduction, results, and conclusions of each article were read and reread carefully until well understood, then summarized on a draft. Once this was done, the selected articles were written in my own words using Microsoft Office Word.
42 total articles were found

15 articles were excluded
- 7 non-English language
- 5 non-melanoma relation to diet

27 articles were included
- 3 prior to the year 2003
- 2 about red meat
- 2 about fish
- 3 about sugar
- 3 about fatty acids
- 6 about vitamins
- 4 about fruits and vegetables
- 1 about alcohol
- 4 about coffee
- 2 about green tea
4. Results

A total of 42 articles were found during the initial search. Upon applying the inclusion and exclusion criteria, 27 studies were found to be relevant to fulfill the inclusion criteria and 15 studies were excluded due to fulfilling the exclusion criteria.

4 articles were related to coffee and their relation to CMM.
2 articles mentioned the relation between green tea and CMM.
1 article summarized the effects of alcohol on CMM.
4 articles were about fruits and vegetables relation to CMM.
6 articles summarized the relation between vitamins A, D, C, and E with CMM.
3 articles examined the effects of fatty acids on CMM.
3 articles mentioned the relation of sugar and CMM.
2 articles were related to fish and CMM.
And 2 articles mentioned the red meat effects on CMM.

The following sections present the results of the articles that were included in the systematic review.

A) Coffee:

Coffee is one of the most popular drinks world-wide. It is available in every country and for every nation around the world. Limited previous studies have yielded conflicting results, some studies showed an inverse relation between coffee consumption and risk of melanoma [24], while others showed no association [25].

In one meta-analysis study that combined three previous researches made on the association between coffee intake and melanoma risk has shown that coffee generates a positive biological effect in our body which in turn protects us from the UV-induced skin cancer [26].

In vivo and animal studies have shown that caffeine obtained from different sources of drinks including coffee and tea can act as an anti-cancer compound, and can inhibit UV-induced carcinogenesis by generating DNA methylation, oxidative damage, and by promoting apoptosis of cancer cells [27].

In other study which was made in Norway by the Norwegian Women and Cancer (NOWAC), some very interesting result concerning coffee consumption were found. A self-questionnaire for 104,080 women with a follow-up information collected 6-8 years later was made. Results showed that coffee contains biologically-active substances that suppress carcinogenesis, which in turn fights melanoma development.

It was concluded from the same study that compared to light consumption of coffee (\(\leq 1\text{ cup\text{]}d\text{)}), low-moderated consumption \((>1\text{-}3\text{ cups\text{]}d\text{)}\) was associated with lower risk of melanoma, while high-moderate consumption of coffee \((>3\text{-}5\text{ cups\text{]}d\text{)}\) was associated with a stronger inverse relation of melanoma development.

In other words, data from NOWAC showed a melanoma risk reduction with the increased of coffee intake on a daily basis [28].
B) Green tea:
Green tea is known as a popular and healthy drink. It is largely consumed in Asian countries such as Japan, China, Korea, and parts of India, and a few countries in North Africa and the Middle East [29]. The consumption of green tea is also increasing in Europe and in the United States because of new investigations showing the health benefits and anti-carcinogenic activities of green tea on various organs.

The anticancer activity of green tea is mainly due to the activity of green tea polyphenols (GTPs) in our body, this natural compound protects us from the UV-induced DNA damage and enhances skin DNA repair by induction of interleukin (IL)-12 which has been shown to have DNA repair ability [30].

In one research which was made back in 2015, researchers examined the association between the effects of GTPs and melanoma development by using different human melanoma cell lines in an *in vitro* environment. It was found that GTPs significantly inhibited melanoma cell lined growth as well as colony formation ability of melanoma cells. It was also found that this inhibition of melanoma growth is dose-dependent; meaning the more GTPs applied on melanoma cells in a test tube, the more inhibition of further cells growth was established.

The mechanisms by which GTPs prevented melanoma growth was detected using Comet assay or single cell gel electrophoresis assay (SCGE). It was found that GTPs exhibits a strong cytotoxic effect by inhibiting histone deacetylase (HDAC) activity, reducing the levels of class I HDAC proteins, increasing activity of histone acetyltransferase (HAT) and inducing DNA damage in melanoma cells, which in turn enhanced the apoptosis of melanoma cells [31].
C) Alcohol:
Alcoholic drinks were used since the dawn of history in celebrations and special events. “Alcohol make you happy”, is a sentence I have heard over and over during my life.
There are more than 17 million adults with some kind of alcohol use disorder (AUD) in 2012, according to the National Institute of Alcohol Abuse and Alcoholism (NIAAA) [32].
Considering the effect of it on our body, there are no two persons who could argue about the fact that alcohol can have a bad effect on our health such as slowed reflexes and motor functions, reduced coordination, impaired thinking and memory, poor judgement, and much more impairments. These negative effects occur every single time one drinks, even a single beer. The more one drinks, the stronger these negative effects [33].
Many studies in recent years have investigated the relationship between alcohol intake and melanoma risk, with result being conflicting. Some studies suggested protective effects, while the majority of studies have shown increased risk of cancers with increased consumption of alcohol over a long period of time.
A new study which was made in 2018 included 20 independent studies that were published during 1986-2016, and included 10,555 melanoma cases. Findings suggest that alcohol drinking may be moderately associated with increased melanoma risk [34].
D) Fruits and Vegetables:
It is well known that fruits and vegetables supply us with a variety of vitamins and good natural sources which regulate our body and promote our health. Many studies were made in the past several decades examining the effect of fruits and vegetables on the prevention of cancer.
The results of the articles concerning fruits and vegetables and their relation to melanoma development were conflicting. Some results showed a protective effect against melanoma, while others showed increased risk of melanoma with increased consumption.
Apigenin is a natural compound found in several plant-based diets such as vegetables and fruits. A big number of studies were made over the past couple of years which showed that this particular natural compound has strong antioxidant, anti-inflammatory, and anticancer properties. Therefore, apigenin has attracted the attention of scientists around the world as a possible chemotherapeutic agent [35]. The anticancer action of apigenin is exhibited by inhibiting the cell cycle, diminishing oxidative stress, improving the efficacy of detoxification enzymes, inducing apoptosis, and stimulating the immune system [36].
In the other hand, in one of the studies which assessed the bad effect of vegetables and fruits on the risk of melanoma, and especially citrus fruits such as lemon and orange, it was mentioned that citrus fruits contain a compound that acts as phototoxic, and it increases the incidence of melanoma. Psoralen, which is the parent compound in a family of natural products known as furocoumarin [37], are found naturally in citrus fruits and other plants as well as many plant-based drugs found in the market. Furanocoumarins are responsible for the majority of phototoxic reactions in humans caused by plants [38]. These compounds can interact with DNA, inhibiting DNA synthesis and cell division [39].
In a study made in the United States, two cohorts of the Nurse’s Health Study were made to assess the effects of dietary vitamin intake on melanoma risk. It was found that orange juice drinking was positively associated with the increased risk of developing skin cancer. The reason for that is the high amount of psoralen compounds (such as furocoumarins) found in citrus fruits, which undergo interaction with photons from the sunlight to create mutational lesions that later on, may develop to melanoma and other skin cancers [40].
E) Vitamins

Vitamins are essential nutrients for our health. The best way to get enough vitamins is to eat a balanced diet with a variety of foods. In some cases, for example when you have low levels of certain vitamins, you may need to take vitamin supplements. The relation between melanoma and vitamins was under investigation for many decades, with results showing that a balanced diet consists of vitamin A, D, C, and E, may reduce the prevalence of CMM.

A case-control study which was carried out between 2012 and 2013 for the treatment of patients with CMM by conducting a food frequency questionnaire. Participants were asked to report their usual frequency of consumption of each food from a list of 36 different kinds of food. It was found that preformed vitamin A (retinol) is necessary for the cell proliferation regulation, and can reduce the incidence of skin cancer in animals exposed to UV light. Retinol precursors, along with antioxidant nutrients, are important components of fruits and vegetables and may be responsible for the anti-cancer effects of these foods.

The same study had found that butter and oregano, which are rich in vitamins A and D may act as a protective risk factor for melanoma [41]. Vitamin D3 has been successfully used at high doses (10,000 units per day) in the treatment of cancer and in the treatment of various autoimmune diseases [42]. Thus, vitamin D3 can be used in the treatment of melanoma at high doses as well, and for all types and stages of melanoma (I, II, III, and IV) [43].

In another systemic review which was made across European countries in 2014, vitamin D was investigated in relation to skin cancer [44]. It was found that in vitro, vitamin D has an anti-cancer effect by inhibiting the growth of malignant melanoma cell lines, by regulating cell proliferation, and by inducing apoptosis of tumor cells [45]. The anti-cancer effect of vitamin D is most likely due to the activation of vitamin D receptors (VDRs) which play an important role in the DNA damage repair. Results of the same study showed that an impaired function of VDRs increases cellular proliferation and decreases differentiation of keratinocytes, and this in turn is reflected by increased susceptibility of epidermal cells to carcinogenesis [46].

When considering other vitamins, it is important to note that vitamin C which is found mainly in citrus (citron, lemon, lime, orange, and grapefruit) as well as many other fruits, is considered to be a protective factor against coronary heart disease, autoimmune diseases, and different types of cancer (including melanoma) [47].

In one interesting study, and for the first time, researchers have investigated the anti-melanoma effect of vitamin E in vivo. It was found that vitamin E inhibited melanoma growth in mice. Prior to this study, it was well known that vitamin E succinate (VES), an ester analogue of vitamin E, inhibits the growth of melanoma in vitro only. Results of this study showed that vitamin E promote melanoma cells apoptosis [48].
F) Fats:
Fats have many important functions in our body. Energy production, keeping the body warm, building-up cells, organs protection, aiding in vitamins absorption from the GI, and hormones production are some of the main functions of fats [49].

"Fat" used to be a bad word when talking about nutrition. Couple of decades ago, your doctor might have recommended that you limit or avoid fat in your diet to prevent weight gain and health problems such as cardiovascular diseases and diabetes. Now doctors know that not all fats are bad. In fact, some fats lower your cholesterol level and help keep you healthy. The key is to get a good balance of fats and other nutrition in our diet.

There are 2 main types of fats, the saturated fats which are solid at room temperature, and the unsaturated fats which are liquid at room temperature. The saturated fats raise the level of the “bad fat”, or the LDL, and they are found mainly in food like red meat, skin of chicken, milky products, butter, and eggs. The unsaturated fats raise the level of the “good fat”, or HDL, and they are found mainly in food like avocado, olive oil, and nuts [50].

The first thought about the use of dietary fats in treating skin disease was made by the historic study of Burr and Burr in 1929. Back then, rats fed with all kinds of fats have experienced retardations, reproductive failure, and skin eruption. One of the investigators of this early experiment found he could treat his hand dermatitis by consuming polyunsaturated fatty acids, originally known as vitamin F. Later on, these fatty acids came to be known as essential fatty acids (EFAs) because humans lack the enzymes necessary for their synthesis in vivo [51].

Linoleic acid (18:2ω6) and α-linolenic acid (18:3ω3) represent the major fats of the polyunsaturated (the good) fatty acids. They are found mainly in various kinds of oils such as liver oil, fish oil, and many types of seeds such as almonds. These fatty acids are considered to be a useful adjunctive treatment for many skin disorders, including atopic dermatitis, psoriasis, acne vulgaris, systemic lupus erythematosus, non-melanoma skin cancer, and melanoma. The mechanisms of the preventive role of polyunsaturated fatty acids in protecting our skin from various diseases are possibly due to elevation of the sunburn threshold, maturation and differentiation of the stratum corneum, inhibition of pro-inflammatory cytokines (tumor necrosis factor-α, interferon-γ, and interleukin-12), inhibition of lipooxygenase, promotion of wound healing, and promotion of apoptosis in malignant cells, including melanoma [54].

In one very interesting experiment made in Korea, a big number of mice were divided in two groups, one group was the control-diet (CD) group, and the other was the high-fat-diet (HFD) group. Tumor cells were injected into the right rear flanks of mice in order to look for the difference in the progression of these cells in the two groups. 16 weeks later results showed that the HFD feeding mice significantly increased in body weight if compared to that of the CD group. The tumor growth was also different between the two groups, the accumulation of tumor cells was higher in the HFD group than in the CD group. Metastasis of the tumor cells to lymph nodes and other organs of the mice was found to be higher in the HFD group compared with the CD group [55].
G) Sugar:
Sugar comes mainly from food rich in carbohydrates. Our body uses sugar in the form of energy. Insulin is a hormone that moves sugar from blood into the cells for energy production and storage [56].
Previous studies have shown that insulin resistance is associated with increased risk of melanoma, patients with skin cancer usually have insulin function deficiency [57]. There are 2 parameters that can indicate the quantity and quality of carbohydrates in our body; Glycemic index (GI), and Glycemic load (GL). GI and GL in high values are proved to be associated with the increased risk of different cancers, type 2 diabetes mellitus, as well as many other metabolic diseases.
Low GI diet compared with high GI diet can lead to lower insulin output and in turn to lower inflammatory response and lower risk of many chronic diseases, including cancer. Both low glucose values and insulin output seem to be anti-inflammatory, while in the other hand hyperglycemia increases the pro-inflammatory process and negatively affects the immune system [58].
In 2017, and for the first time, a case-control study presented the association between GI and GL with the risk of melanoma. The study was carried out in Italy where 380 melanoma patients and 719 controls were involved. Food questionnaires related to diet containing high amount of carbohydrates were used to assess the dietary habits of the patients. It was found that high risk of melanoma is associated with higher intake of starch (white bread, white rice, pasta, and noodles are among foods containing high amount of starch). In the same study it was concluded that GL in high values increases the risk of developing melanoma, but GI has no association with melanoma risk [59].
**H) Fish:**
Fish, is a food known of its health benefits on our body. It is rich in good fatty acids as well as high amount of proteins that are essential for a good immune system function. During my search of articles related to fish and melanoma development, I have found 2 contradicting results. The first one that fish is rich in long-chain n-3 polyunsaturated fatty acids (known as omega-3 fatty acids) which promotes an anti-cancer action against many types of cancers including melanoma [60]. In the other hand, I have found that Polychlorinated biphenyls (PCBs), mainly from fatty fish, may promote melanoma progression due to the toxicity they exhibit. PCBs are synthetic organochlorine chemicals which is absorbed, distributed into the body, and then accumulate in adipose tissue of different animals including humans. Their half-life ranging from couple of years to decades [61].
I) Red meat:
Analysis of lifestyle behaviors such as diet consumed, physical activities, and smoking questionnaires were collected from 249 patients with melanomas more than 1.00 mm thick. Results of this study showed that red meat consumption more than 3 times per week was associated with worst outcomes [62].
In another big study the relation between processed meat and melanoma was investigated. Dietary information was assessed using food frequency questionnaires in two prospective cohorts – 75,263 women from the Nurses’ Health Study (1984 – 2010) and 48,523 men from the Health Professionals Follow-up Study (1986 – 2010). Results showed that when consuming red and processed meat more often, risk of melanoma development is increasing [63].
5. Discussion

It is suitable to say that for everything in our life there are the good and bad sides. Except for the perfection of God powers. Even diet itself when consumed too much, can have a negative effect on our health. The balance of diet is very important in order to balance our body metabolism, and it can be achieved by a good education and knowledge.

Is there any relation between diet and skin diseases such as cutaneous malignant melanoma (CMM)? This was the main question and topic of my systemic review. Answering the question was a challenging task due to various dietary habits I had to go through in order to collect the right information that could shape my article. Initially, it seemed hard to define whether diet can be a risk factor for skin diseases. But when I started reading articles the whole idea shaped itself, the relation between the two and the mechanisms by which diet affects CMM were understandable.

Since the early 90’s it was well known that food we eat may serve as an adjuvant treatment for various diseases affecting us. Up-to-date experts from all over the world investigated this hypothesis deeply and carefully in order to have a better idea about diet we consume such as vitamins, fats, sugar, coffee, tea, vegetables, fruits and many other dietary habits, and the way they can affect us by preventing or enhancing the risk of CMM.

Working on my thesis, I have found that vitamins such as vitamin D, C, E, and F can act as protective factors against CMM. The same can be seen looking at the effects of coffee and tea which supply us with biologically active substances that fight CMM cells growth.

Concerning saturated or trans-fats and sugar which are associated with increased Body Mass Index (BMI), negative effects were found. CMM growth was enhanced in populations consuming processed or red meat, saturated fats, sugar, and alcohol more than usual. In the other hand poly-unsaturated fats and mono-unsaturated fats, vitamins, coffee, and green tea were associated with protective effects against CMM. The question whether diet can act as a savior or a harmful factor in relation to skin cancer will be open for investigation for many decades to come. The mechanisms by which food can protect us from various diseases are still to be examined and discussed by scientists.
6. Conclusions

Considering the fact that CMM risk factors are mainly due to high exposure to UV radiation together with many genetic factors which play a role in the disease development, studies showed that diet can be a key risk factor.

A. Coffee has biological molecules that protect us from the UV-induced carcinogenesis by generating DNA methylation, oxidative damage, which in turn promotes cancer cells apoptosis.

B. Green tea is rich in green-tea-polyphenols (GTPs) that protect us from the UV-induced skin damage by enhancing interleukin-12 which is proved to have DNA repair abilities.

C. Alcohol relation to CMM showed conflicting results, some studies showed protective role, while the most recent study (2018) which included 10,555 melanoma cases showed moderately increase in CMM risk with consumption of alcohol more than the daily allowed dose for men and women.

D. Vitamins are essential for our health, many studies showed protective roles of vitamins A, D, C, and E against CMM. Vitamin A is an antioxidant which protects skin DNA and promotes a better regulation of cell proliferation. Vitamin D3 given in high amounts can be used as an adjuvant treatment against CMM. This effect is expressed by regulating cell proliferation and increasing cancer cells apoptosis. Vitamin C is proved to be a strong antioxidant which protects us from various diseases including coronary heart disease, autoimmune diseases, and many cancers including melanoma. Vitamin E inhibits melanoma growth in vivo and in vitro.

E. Fruits and Vegetables showed conflicting results. The protective role of fruits and vegetables is mainly due to Apigenin, a natural compound which is a strong antioxidant and anti-inflammatory. The anticancer effects of Apigenin is expressed by regulating cell cycle, diminishing oxidative stress, and improving efficacy of detoxification enzymes work in our body. In the other hand fruits and vegetables were shown to increase risk of CMM because they contain a compound called furocoumarin, which is responsible for the majority of phototoxic reactions in humans cause by plants. Furocoumarins interact with DNA inhibiting DNA synthesis and promoting carcinogenic effects.

F. Fats are of 2 main types. The first is the mono/polyunsaturated fats which showed protective roles against CMM and can be used as an adjuvant treatment for many types of skin diseases such as atopic dermatitis, psoriasis, SLE, non-melanoma skin cancer, and melanoma. The anti-cancer effects of the unsaturated fatty acids are expressed by elevation of the sunburn threshold, inhibition of pro-inflammatory cytokines, promotion of wound healing, and cancer cells apoptosis.
The other major type of fats is the saturated one. They are the “bad” fats which increase the body weight when consumed in high amounts. Studies showed that increased body weight increased the risk of developing melanoma skin cancer as well as increased risk for the diseases metastasis to regional or distal lymph nodes.

**G. Sugar** is shown to increase the risk of CMM when consumed in high amounts. Insulin resistance increases the risk of CMM development. High values of glycemic load (GL) and glycemic index (GI) increase the risk of CMM development as well.

**H. Fish** showed conflicting results, which the protective role against CMM is seen mainly due to the omega-3 which is proved to be an anti-cancer compound by promoting cell cycle regulation and skin DNA protection against UV light carcinogenesis. In the other hand fish meat contain a synthetic organochlorine chemicals found in the environment and are called polychlorinated biphenyls (PCBs). Studies showed that these compounds accumulate in our body fatty tissues and increase risk of CMM development.

**I. Red meat** and processed red meat are shown to increase CMM development risk when consumed more than usual.
7. Conflict of interest

The author states that there are no conflicts of interest to declare.
1. Atypical Moles (Dysplastic Nevi).
Can be found at: https://www.skincancer.org/skin-cancer-information/atypical-moles

2. Melanoma. What is melanoma?
Can be found at: https://www.skincancer.org/skin-cancer-information/melanoma

3. Understanding melanoma. Melanoma stats, facts, and figures.
Can be found at: https://www.aimatmelanoma.org/about-melanoma/melanoma-stats-facts-and-figures


5. Superficial spreading melanoma. Know the signs.
Can be found at: https://www.healthline.com/health/superficial-spreading-melanoma

6. Types of melanoma. The four basic types.
Can be found at: https://www.skincancer.org/skin-cancer-information/melanoma/types-of-melanoma

7. What is melanoma skin cancer?
Can be found at: https://www.cancer.org/cancer/melanoma-skin-cancer/about/what-is-melanoma.html

Can be found at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3074354/


Can be found at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3874946/

Can be found at: https://www.ncbi.nlm.nih.gov/pubmed/27416086

Can be found at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC526387/

Can be found at: https://www.ncbi.nlm.nih.gov/pubmed/24485530

14. Melanoma signs and symptoms.
Can be found at: https://www.aad.org/public/diseases/skin-cancer/melanoma#symptoms.

15. The EBCDEs of melanoma.
Can be found at: https://www.melanoma.org/understand-melanoma/diagnosing-melanoma/detection-screening/abcedes-melanoma
16. TNM classification of malignant melanoma. The American Joint Committee on Cancer (AJCC) tumor/node/metastasis (TNM) classification and staging system for cancer. Can be found at: https://emedicine.medscape.com/article/2007147-overview


32. The Effects of Alcohol on the Body. Can be found at: https://americanaddictioncenters.org/alcoholism-treatment/body-effects/


50. What types of fat are in food? Can be found at: https://www.webmd.com/diet/guide/types-fat-in-foods#1


37. Psoralen. Can be found at: https://en.wikipedia.org/wiki/Psoralen


56. What is glucose? Can be found at: https://www.webmd.com/diabetes/glucose-diabetes#1


