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Olive trees and incidence of breast and colorectal cancers: A Systematic review

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Abstract
Introduction: *The aim of this systematic review was to find the role of olive in preventing or inhibiting breast / colorectal cancers; and specify which part of the olive tree is most efficient.*
Methods: *Only 14 full text eligible articles were included. PRISMA checklist was used. Also, attention was paid for bias sources.*
Results: *Studies were categorized into three categories: experimental, observational, and reviews. It was found that 9 out of 14 studies of breast cancer demonstrated or suggested that olives had a protective role, and 2 studies demonstrated an inhibitory role. The 3 reminder studies suggested both protective and inhibitory roles. Also, 3 studies of colorectal cancer were included. Two studies had shown an inhibitory role, while the third study presented protective role.*
Discussion: *The inconsistent association between olives and risk of cancer could be due to the fact that people eat mixtures of foods with different nutrient contents that may interact synergistically. Both olives and olive oil contain essential amounts of other compounds considered anticancer agents. Moreover, Oleuropein inhibits cell growth, and has direct anti-tumor effects.*
Conclusion: *The role of olive was mainly protective, and the most effective part was the olive oil, even fried olive oil*
Keywords*: breast cancer, colorectal cancer, olive tree, olive oil, systematic review.*

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I. Introduction

1.1 Rationale

Jerash governorate is a hilly region with fertile lands, located north west of Jordan. It has the smallest area of the 12 governorates, yet it has the second highest density (447.5 / km^2), and ranked 7th governorate by population (in 2011, population in Jerash governorate was 187500 persons). In 2012/2013, a two-stage cluster study, about environmental health assessment of water shortage, was implemented in Jerash governorate. It was found that there was high level of nitrate in some water resources, above the national standard for drinking water (50.0 ppm). This was expected because Jerash governorate is an agricultural area, hence nitrogen-fertilizers used excessively by farmers, result in natural existence of nitrate in ground water. Notably, almost one-fourth of the total area was covered with olive groves; and number of olive trees was about two million trees [1].

Surprisingly that the incidence of cancer in Jerash governorate, during 2000-2011, was 3.8 per 10,000, which was about half of Jordan national incidence rate. And though the most common type of cancer was breast cancer among Jordanian females, and colorectal cancer among Jordanian males, but in the study area (in Jerash governorate) these two types were not found. Only 16 household dwellers in the sample (810 participants) suffered from cancer. Though the number seems very low, but it was reasonable, since on the average, during 2000-2011, every 10,000 Jordanian persons (all over the country)7 had cancer. Leukemia cancer was the dominant type among cancer patients in the sample, followed by an equal percent of bones, digestive system, neuroblastoma, and skin cancer [1].

Based on the previous results of the study, a common-sense question floats : does olive trees play a significant role in lowering or preventing breast cancer and colorectal cancer in Jerash governorate? And which part of the olive tree could be more efficient : the olive oil, the olive fruit, or the leaves? These questions were motives to make the systematic review, hopeful to find answers.

1.2 Objectives

The aim of the systematic review was to:
1-find significant answers related to the role of olives in preventing or inhibiting breast / colorectal cancers.
2-specify which part of olive tree is more efficient in lowering or preventing breast/ colorectal cancer.

II. Methods

2.1 Protocol and registration

After identified the study questions, all articles in SDL (Saudi Digital library) databases, and in PubMed database were indexed with "olives and cancer" terms. 22238 articles in SDL and 35 articles in PubMed databases were identified. However, 27 eligible article abstracts were screened, 13 of them did not have full text. Therefore, only 14 full text eligible articles were included.

PRISMA checklist was used for writing the protocol of systematic review (http://www.prisma-statement.org/Protocols/Registration.aspx). While the registration number (70646) was obtained from PROSPERO (International prospective register of systematic reviews) (https://www.crd.york.ac.uk/PROSPERO/).

2.2 Eligibility criteria

Articles in English, and relevant to relationship between olives and breast/colorectal cancers, were included. No matter year of publication.

2.3 Information sources

Databases used were PROQUEST, EBSCO, Wiley online library, Springer, Elsevier, Oxford, and PubMed.

2.4 Data collection process

Data extraction from each eligible article included the title, name of authors, year of publication, type of study, limitations, bias and key findings. At the end, all data was gathered in one table, to make thorough review and comparison.

2.5 Risk of bias in individual studies

Four domains may introduce bias into a systematic review: study eligibility criteria; studies identification and selection; data collection and study evaluation; synthesis and findings [2]. Therefore, attention was paid for bias sources in eligible articles, specially reporting. Furthermore, outcome reporting or selective reporting bias, was one of the most major biases affecting individual studies results.

III. Results

The method used for selection studies, inclusion and exclusion some of them was depicted in fig.1. The included studies were miscellaneous. So, they were categorized into three categories : experimental, observational, and review studies. In each category, studies were classified. For experimental, there was clinical, in vitro, and animal models. For observational, there was case-control, and ecological studies. Finally, for review studies, there was systematic and non-systematic review studies. A summary of the selected studies according to the author, year published, design, key findings was presented on table 1.

3.1 Experimental studies

3.1.1Clinical trial

A randomized, single-blind, controlled trial conducted at primary health care centers in Spain. From 2003 to 2009, 4282 women aged 60 to 80 years and at high risk of cardiovascular disease were recruited. The study was to assess the effect of two interventions with Mediterranean diet on breast cancer incidence. Participants were randomly allocated to a Mediterranean diet with extra-virgin olive oil, a Mediterranean diet with mixed nuts, or a control diet with an advice to reduce fat. After a follow-up of mean 4.8 years, 35 cases of breast cancer were confirmed. The results of the study suggested a beneficial effect of a Mediterranean diet with extra-virgin olive oil in primary prevention of breast cancer. However, these results need to be confirmed in longer-term and larger studies. [3].

3.1.2 In vitro human cells

An experimental control study, used the main olive oil polyphenols, Oleuropein (OL) and hydroxytyrosol (HT), which possess anti-proliferative effects. It was concluded that the main

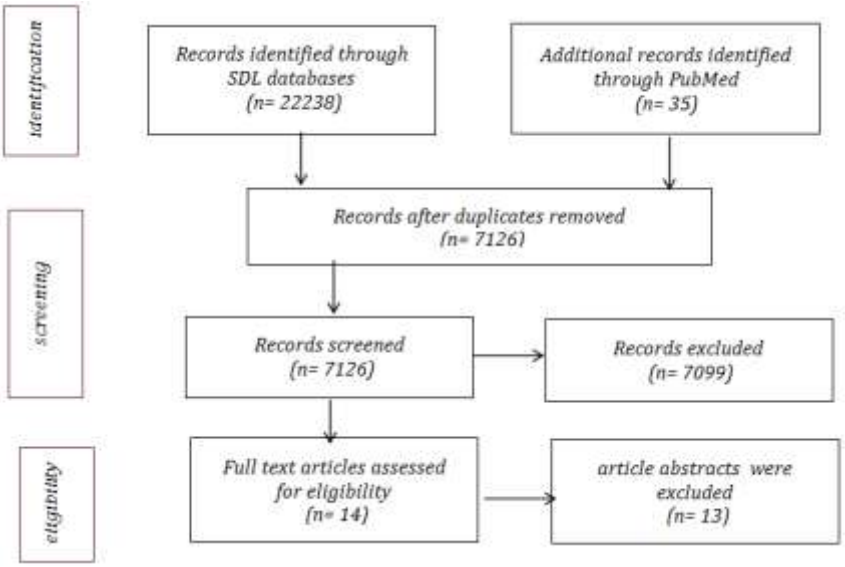

Figure 1 Flow chart of systematic review process

effects on cell growth are mediated by FAS (Fatty acid synthase, a key anabolic enzyme of biosynthesis of fatty acids) in certain human colorectal cancer cell types. The findings suggested that more differentiated and specialized cells could be more able to control the genes expression which involved in cell reproduction [4].
Another in vitro study, studied the effects of hydroxytyrosol HT and tyrosol TY (two of the major phenols present in virgin olive oils) on human breast cell lines. HT was described as an antioxidant compound with higher activity than TY, and related to the prevention of breast cancer. But they can interact with each other, so increase or inhibit the effects of each component alone. The results showed that regarding the prevention of breast cancer, HT and TY failed to affect cell reproduction rates, cell cycle profile or cell death in human mammary epithelial cells (MCF10A) or breast cancer cells (MDA-MB-231 and MCF7). Interestingly, HT prevented oxidative DNA damage in the three breast cell lines. Therefore, findings suggested that simple phenol hydroxytyrosol could contribute to lower incidence of breast cancer in populations who consume virgin olive oil [5]. Future work was needed to investigate if the effects synergetic or inhibitory. Also, methods to control bias should be clearly described.

3.1.3 Animal models

In this study, data from sixteen experimental series in an animal model, about the Mediterranean diet, olive oil and breast cancer risk was followed. It was found that diets rich in extra virgin olive oil (EVOO) had negative modulatory effect on experimental breast cancer or weak promoting effect, much lower than effects of a high-corn oil diet. EVOO stimulated different molecular changes in tumours, like activity of signalling proteins and gene expression. These modifications could prompt lower proliferation, lower DNA damage, and higher apoptosis. Therefore, consumption of extra virgin olive oil in moderate quantities and throughout the lifetime may reduce breast cancer risk [6]. However, this study has limitations such as methods used to avoid bias were not discussed, nor wrote limitation of experiments. Also, the content and conclusions were not well written.

3.2 Observational studies

3.2.1Case-control studies

A case-control study conducted in the San Francisco Bay area, in which 1,703 breast cancer cases diagnosed between 1995 and 1999 and 2,045 controls were included. Intake of total fat, types of fat, and preferred use of fat for cooking were assessed. It was found that high fat intake was associated with increased risk of breast cancer. A positive association was found for oleic acid, but not for linoleic acid or saturated fat. Also, risk was increased when cooking with hydrogenated fats, or vegetable/corn oil (rich in linoleic acid) compared to those used olive/canola oil (rich in oleic acid). The results suggested that a low-fat diet may play a preventative role in breast cancer. This could be due to monounsaturated trans fats [7]. Methods to control bias sources were described; however, recall bias and measurement errors were hard to control.

Another multicentric case-control study about the relation between fried foods and colorectal cancer risk was investigated in Italy and Switzerland, between 1992 and 2000. There was1394 cases of colon cancer, 886 cases of rectal cancer and 4765 controls. All the cancer cases were confirmed. Controls were patients admitted to the same hospitals, but for acute, non-neoplastic conditions, not relevant to digestive tract diseases.

It was found that only olive oil appeared to protect from colon cancer risk. In addition, results did not indicate a relevant role of fried foods on colorectal cancer risk. So, it may concluded a possible favorable effect of (fried) olive oil on colon cancer risk, but not on rectal cancer risk [8]. However, to confirm these conclusions, longer-term and larger studies should be implemented.

3.2.2 Ecological studies

An ecological study, with 28 countries from four continents was conducted. Age adjustment was used before comparison, then existing international databases, incidence rates for colorectal cancer (CRC), food supply data, and olive oil consumption data , were extracted, from published sources, combined, and analyzed. Associations between CRC and 10 dietary factors were calculated. It was found that 76% of the intercountry variation in CRC incidence rates was explained by significant dietary factors-meat, fish and olive oil-in combination. Meat and fish were positively associated, while olive oil was negatively associated, with colorectal cancer risk. Therefore, the conclusion was that Olive oil may have a protective effect on the development of CRC [9].

3.3 Review studies

3.3.1 Systematic review

A systematic review and a meta-analysis of 13800 patients and 23340 controls in 19 observational studies were applied. Original research studies about Mediterranean diet, olives oil and different types of cancer, published in English, between 1990 and March 1, 2011 were selected. The focus was only on studies that solely assessed raw olive oil intake, in order to eliminate the synergistic effect of cooking. Heterogeneity was assessed and evaluated. Also, sensitivity analyses were performed according to some characteristics like: Mediterranean or not and type of cancer. Moreover, the "funnel's plot" was tested. All statistical calculations were performed using NCSS 2004 software. It was found that olive oil consumption was associated with lower odds of developing breast cancer, and a cancer of the digestive system , compared with the lowest intake. The strength and consistency of the findings suggested the protective role of olive oil intake on cancer risk [10]. However, which was responsible for its beneficial effects olive oil's monounsaturated fatty acid content or its antioxidant components was not clear.

3.3.2 Non-systematic review

A review of 58 epidemiological, clinical, and experimental studies from 1993-2017, was performed. This review critically discussed the available literature regarding the anticancer and onco-suppressive activity of oleuropein, and the underlying molecular mechanisms. A research had shown that oleuropein acts as an anticancer agent via several major mechanisms. Also, highly evidence from preclinical studies had shown that oleuropein effectively stimulated complete turn back tumors in mice model. Moreover, The Lyon Diet Heart Study, a first randomized trial with 605 patients intake a Mediterranean diet, showed a decreased cancer risk, after four-year follow up. While PREDIMED was a randomized, single-blind, controlled field trial, consisted of 4282 women aged 60 to 80 years. They were randomly allocated to a Mediterranean diet with extra-virgin olive oil, or with mixed nuts, or intake control diet focused on reduce dietary fat. The intervention group treated with extra-virgin olive oil reported a significant preventive effects against breast cancer [11]. A limitation of this review is that, methods to control bias sources were not mentioned .

Another review consisted of 99 cell and animal models and human intervention studies, was implemented. The aim was to merge the current literature regarding bioavailability and anti-cancer mechanisms involved in Olive leaf extract polyphenol action. Olive leaf extract (OLE) includes a higher quantity and variety of polyphenols than extra virgin olive oil (EVOO). It had been claimed that Olive polyphenols play an important protective role in cancer and inflammation-related diseases. Both inflammatory and cancer cell models had shown that olive leaf polyphenols were anti-inflammatory and protect against DNA damage. The diverse bioactive properties of olive leaf polyphenols may explain the inhibition of progression and development of cancers. Finally, it was concluded that there was strong evidence, from cell models which demonstrated that olive polyphenols, and specifically the combination found in olive leaf, were able to modify and interact with molecular pathways, therefore may inhibit the progression and development of cancer [12].

Moreover, the aim of another review was to revise major clinical and experimental evidences underlining the pharmacological properties of oleuropein on human health. In addition, provided original data on the role of oleuropein in counteracting lipid accumulation in a mouse model of non-alcoholic fatty liver disease. The study included 68 major clinical and experimental evidences from 1973-2014. Accumulating experimental, clinical and epidemiological data had provided support to the traditional beliefs of the beneficial effect of olive derivates. In particular, the polyphenols present in olive leaves, olives, virgin olive oil and olive mill waste were strong antioxidant and radical scavengers, with anti-tumor and anti-inflammatory attributes [13]. It is worth to

mention that this review has many limitations. How to avoid bias risk was not mentioned, nor comments on reviewed studies.

In 2013, Grosso et al conducted a review study, consisted of 107 epidemiological and experimental studies . The aim was to point-out hypotheses on potential relationship between lifestyle factors such as dietary habits, and cancer. The most pooled analyses of epidemiological studies supported strongly the hypothesis that the Mediterranean diet may play a protective role of several types of cancers, especially those of digestive tract, whereas contradictive results were reported for hormone-dependent cancers. Moreover, evidence regarding olive oil and whole grains increased the useful effects of such dietary pattern against cancer. 4.7% of cancers among men and 2.4% in women would be avoided if they had a greater adherence to Mediterranean dietary pattern. However, no data was given for specific cancer risk. Experimental and human cellular studies had provided new evidence on the possibility protective effect of olive oil on certain cancers such as breast, colorectal and prostate cancers. Finally, Olive oil had been suggested to inhibit colon cancer development [14]. It is worth to mention that the researchers made a good effort, and were full aware of limitations of this type of study.

Escrich et al reviewed 113 epidemiological and experimental studies during 1990-2006, to specify the role of olive oil in cancer prevention and progression. Epidemiological studies had shown the potential benefits of olive oil, specifically in relation to cancer risk. The negative modifying effect, probably protective, of high virgin olive oil diets on carcinogenesis had been experimentally manifested. There was evidence that olive oil affects different stages of carcinogenesis, gene expression, hormonal levels, signal transduction path-ways, cell membrane composition, and the immune system. It had been concluded that either the main monounsaturated fatty acid, oleic acid, or the minor compounds as the case responsible for its chemo-protective effects. In addition, bioactive compounds of olice oil were elicited as potential agents in the treatment of cancer [15]. To control bias risk, researchers included all studies regardless offereing significance association or not.

At last, a review study of 35 epidemiological and experimental studies was done. Epidemiological studies of breast and pancreatic cancer in several Mediterranean populations had demonstrated that increased dietary intake of olive oil was associated with a small decreased risk or no increased risk of cancer. Experimental animal model studies of high dietary fat and cancer also demonstrated that olive oil had either no effect or a protective effect on the prevention of tumors [16]. To avoid selection bias, the researcher included both studies that support or not support his hypothesis.

Table 1 A summary of the included studies according to the author, year of publication, design, and key findings

Serial no.	Author	Year of publication	Design	Key findings
1	Toledo et al	2015	randomized, single-blind, controlled field trial	Results suggest a beneficial effect of a Mediterranean diet supplemented with extra-virgin olive oil in the primary prevention of breast cancer
2	Notarnicola et al	2011	Experimental control study	The main olive oil polyphenols have inhibitory effects on colorectal cancer cells growth.
3	Warleta et al	2011	In vitro human cell lines	Simple phenol hydroxytyrosol could contribute to a lower incidence of breast cancer in populations that consume virgin olive oil
4	Escrich et al.	2011	16 Experimental animal series	Diets rich in extra virgin olive oil had a negative modulatory effect on experimental breast cancer to a weak promoting effect
5	Wang et al	2008	Case-control study	A low-fat diet mighty play a role in breast cancer prevention.
6	Galeone et al	2007	case-control study	A possible favorable effect of (fried) olive oil on colon cancer risk but not on rectal cancer risk.
7	Stoneham et al	2000	Ecological study	Olive oil might have a protective effect on the development of colorectal Cancer
8	Psaltopoulou et al.	2011	Systematic review and meta-analysis	Olive oil consumption was associated with lower odds of developing breast cancer and a cancer of the digestive system. However, it was unclear whether olive oil's monounsaturated fatty acid content or its antioxidant components were responsible for its beneficial effects
9	Barbaro et al	2014	a review study of 68 major clinical and experimental evidences from 1973-2014	Studies on experimental animals had determined that oleuropein treatment prevents development of skin, soft tissue and breast cancer
10	Farooqi et al	2017	review of 58 epidemiological, clinical,	Oleuropein acts as an anticancer agent by several major mechanisms.

			and experimental studies	
11	Boss. et al	2016	review 99 cell models and human intervention studies.	Evidence was available in cell and animal models to support the conclusion that OLE does had beneficial effects and there was anecdotal evidence that olive polyphenols had a protective effect against cancer in humans
12	Grosso et al.	2013	Review 107 epidemiological and experimental studies	Mediterranean diet might play a role in preventing digestive tract
13	Escrich et al.	2006	Review 113 epidemiological and experimental studies	Protective role of olive oil intake on breast cancer risk. There was evidence that olive oil influences different stages of carcinogenesis
14	Newmark H.	1997	Review 35 epidemiological and experimental studies	Epidemiological studies of breast and pancreatic cancer had demonstrated that increased dietary intake of olive oil was associated with a small decreased risk or no increased risk of cancer. Experiments in vitro and in animal models suggested a tumor-inhibiting role for high squalene content of olive oil.

IV. Discussion

The main findings of the studies, including the limitations of each study included, if any, were summarized in table 2.

Table 2 Summary of main findings of each study, strength, and limitations

Serial no.	Author	Year	Part of olive tree	The effect	Strength / Limitations
1	Farooqi et al	2017	Extra-olive oil	Protective	Methods to control bias sources were not mentioned
2	Boss et al	2016	Olive leaf	Protective & inhibitory	Methods to control publication bias were not mentioned
3	Toledo et al	2015	Virgin olive oil	Protective	Well organized procedures
4	Barbaro et al	2014	Olive oil and olive leaf	protective & inhibitory	Methods used to avoid bias were not mentioned
5	Grosso et al.	2013	Olive oil	Protective	Methods for selecting studies were missing. How to avoid selection bias was not mentioned
6	Psaltopoulou et al.	2011	Olive oil	Protective	Well organized procedures
7	Escrich et al.	2011	Extra virgin olive oil	Protective	Methods used to avoid bias sources of the experiments were not mentioned
8	Notarnicola et al	2011	Olive oil	Inhibitory	Well organized procedures
9	Warleta et al	2011	Virgin olive oil	Inhibitory	Methods used to control bias were not mentioned
10	Wang et al	2008	Olive oil	Protective	Recall bias and measurement errors were hard to control
11	Galeone et al	2007	Olive oil	Protective	Recall bias
12	Escrich et al.	2006	Olive oil	Protective	Good procedures
13	Stoneham et al	2000	Olive oil	Protective	Good procedures
14	Newmark H.	1997	Olive oil	Protective and inhibitory	Good procedures

4.1The nature of role of olives

For the first objective of this systematic review: as seen in table 1 and 2, with respect to breast cancer, that 9 out of 14 studies demonstrated or suggested that olives had a protective role, and 2 studies –which were in vitro – demonstrated an inhibitory role. The 3 reminder studies –which were all review type- suggested both protective and inhibitory roles.

With respect to colorectal cancer, 3 studies were included. Two studies concluded an inhibitory role, while the third study found significant protective role of olives.

The inconsistent association between olives and risk of breast cancer could be partly due to the fact that people do not eat foods or nutrients separately but mixtures of foods with different nutrient contents that may interact synergistically, result in causing or protecting from cancer. Therefore, assessing diet as a whole will provide more useful information on the role of diet in breast cancer risk [3]. Although experimental studies in animal models had clearly demonstrated an influence of dietary lipids on breast cancer, inconsistent human epidemiological results had been reported. While cohort studies had shown conflicting results, case-control analyses and new prospective studies had shown the effect of high fat intake on breast cancer risk [6].

4.1.2 protective role

Epidemiological and experimental studies had found a relationship between dietary lipids and some cancers, like breast and colorectum [6]. With respect of breast cancer, diet as a modifiable component of lifestyle, could influence breast cancer development. Epidemiological evidence on the effect of specific dietary factors was not conclusive [3].

In Toledo's study, the 1:1:1 clinical trial study was conducted within the frame of the PREDIMED (Prevención con Dieta Mediterránea) trial, for a median follow-up of 4.8 years. PREDIMED is a large, multicenter, randomized trial to test the effects of the traditional Mediterranean Diet on prevention of cardiovascular disease. The mean age of participants was 67.7 years, and mean body mass index was 30.4. Most female participants were underwent menopause before 55 years, and less than 3% of them had hormone therapy. Cancer incidence was a secondary outcome in the original study protocol. Also, five specific cancer locations were followed in all interim analyses and in all reports: breast cancer, colorectal cancer , gastric cancer. lung cancer, and prostate cancer. Breast cancer were the first results for any cancer that have been analyzed. The three trial groups together were assessed, and it was found that participants who attained a higher extra-virgin olive oil consumption during follow-up displayed the lowest risk of breast cancer. In addition, 62% relatively lower risk of malignant breast cancer than those allocated to the control diet [3].

Due to the difficulty in obtaining data with controlled variables in humans, animal models are widely used to have insight into the influence of diet on health. The experimental model of breast cancer chemically induced with 7,12-dimethylbenz ([alpha]) anthracene (DMBA) in the female Sprague-Dawley rat was used. Escrich et al investigated different effects of olive oil and n-6 lipids on mammary adenocarcinomas. They used a low-fat diet (with 3 % of corn oil), a high-fat n-6 diet (with 20 % of corn oil) and high-fat n-9 (included a 17 % of extra virgin olive oil and 3 % of corn oil) diets. It was found that the high-olive oil diet extended a weak stimulatory effect to a protective effect on mammary carcinogenesis. Moreover, in some of the experimental series, they observed that the olive oil diet reduced tumour content and volume which suggested a protective effect of the olive oil [6]. The results were compatible with the non-promoting effect of a diet rich in extra-virgin olive oil [17].

Both the two case-control studies found significant association between olive oil and low cancer risk. One of these two studies was about breast cancer, while the other one was about colorectal cancer. With respect for breast cancer, the study included women from a comparable numbers of Whites, African Americans, and Latinas. In this population-based, case-control study, complementary approaches to assess the effects of different types of dietary fats on breast cancer risk were used. Cases were women aged 35 to 79 years with a first primary incursive breast cancer diagnosed between 1995 and 1999 were identified through the Greater Bay Area Cancer Registry. While controls were identified through random digit dialing and were frequency matched to cases according to the expected race/ethnicity and 5-year age distribution of cases. Telephone screening interview, self-report, and in-person interview had been used. Also, the interviewers took 3 measurements of height and 2 measurements of weight. The results found a positive association between total or monounsaturated fat and breast cancer risk only among Whites and Latinas but not among African Americans. Moreover, it was concluded that diet may play a role in reducing breast cancer risk [7]. This is consistent with A case-control study of a total of 755 women, that designed to assess the role of differential fatty acid intakes and olive oil consumption on breast cancer risk in the Canary Islands. It was conducted between 1999 and 2001[18].

With respect of colorectal cancer, Galeone's study included cases of colon cancer (median age 62 years), from Italy and from Switzerland; cases of rectal cancer (median age 63 years), from Italy and from Switzerland. while controls were patients admitted to the same hospitals for acute, non-neoplastic conditions unrelated to digestive tract diseases, from Italy and from Switzerland (median age 58 years). Trained interviewers questioned cases and controls during their stay at hospital. Researchers evaluated the fat used for frying, and found that only olive oil appeared to protect from colon cancer [8]. This indicated that olive oil is more stable in comparison with other vegetable oils [19]

For the ecological study, the systematic review study, and 6 out of the 7 review studies suggested a protective role of olives. This is consistent with a systematic review which reviewed epidemiological studies on olive oil and cancer published up to 2010, in the Medline database . After assessment of relevant papers, 25 studies were included, and a meta-analysis of studies of breast cancer were performed. The summary relative risk of breast cancer was 0.62 (95% CI, 0.44-0.88) for the highest versus lowest level of olive oil consuming [20]. This is consistent with many epidemiological studies, which suggested that olive oil intake is associated with a reduced risk of cancer [21].

4.1.2 Inhibitory role

There was two studies that support the inhibitory role of olives, for breast and colorectal cancer. Interestingly, both studies were in vitro human cells. For colorectal cancer, fatty acid synthase (FAS) enzyme gene expression ,and activity , in treated hydroxytyrosol -29 and SW620 cells, were evaluated. It was found that

the inhibition of Cell growth, detected after treatment of hydroxytyrosol (HT)-the main olive oil polyphenols-, was mediated by an inhibition of FAS expression and its enzymatic activity in SW620 cells, while the anti-protective effect in HT-29 cells was independent from FAS. Also, the main olive oil polyphenol, Oleuropein spent an anti-reproductive effect only on SW620 cells with a mechanism which excluded FAS [4]. For breast cancer, hydroxytyrosol acts as an efficient free radical scavenger, but did not affect cell production rates, cell cycle profile or cell death in human mammary epithelial cells or breast cancer cells . It was found that hydroxytyrosol decreased the intracellular reactive oxygen species level in MCF10A cells. Interestingly, hydroxytyrosol prevented oxidative DNA damage in the three breast cell lines [5]. This is consistent with in vitro study which evaluated the effects of Oleuropein on hydroxityrosol (HT)-29 human colon adenocarcinoma cells, and to demonstrate the anticancer molecular mechanisms engaged [22].

4.1.3 Both protective and inhibitory role

All the three studies that support simultaneous the protective and inhibitory properties of olive oils, were review type. The literature identified by Boss et al (2016) for review included Olive leaf polyphenols, bioavailability of olive leaf polyphenols, olive leaf properties that protect against development and progression of cancer. There was strong evidence from cell models that olive polyphenols, and specifically the combination found in olive leaf, were able to modify and interact with molecular pathways and in doing so may inhibit the progression and development of cancer. Oleuropein and HT were consistently reported to differentiate between cancer and normal cells; inhibiting reproduction and inducing death only in cancer cells . The challenge in cell models to in vivo, arises when considering bioavailability of the polyphenols. This could explain why olive oil protective effects in humans show a strong association with cancers of the digestive system. In other cancers olive oil phenolics had been suggested to act as phytoestrogens and anti-inflammatory agents, thus producing a protective effect [12].

The literature identified by Barbaro et al (2014) for review included Effects of Oleuropein on Human Health, like antioxidant Effect, anti-inflammatory and anti-atherogenic effects, anti-cancer and anti-angiogenic effect, antimicrobial and antiviral effects. Several mechanisms had been proposed for the anti-tumor properties of the virgin olive oil. Olive oil might reduce environmental and food carcinogens bioavailability. Most importantly, virgin olive oil might protect cells from oxidative stress. This is due to high content of oleic acid, which is less susceptible to oxidation, and for high content of hydroxytyrosol and oleuropein. Among the minor antioxidants present in olive oil and olives, oleuropein had been indicated as the one responsible for the major anti-tumor activity. Oleuropein as anti-cancer compound, targets multiple steps in cancer progression. It might protect cells from incurring genetic damage leading to cell death, and can prevent tumor progression [13].

Finally, Newmark et al (1997) proposed that the high squalene content of olive oil was a major factor in the cancer risk-reducing effect of olive oil. They found a few experiments in vitro and in animal models suggested a tumor-inhibiting role for squalene. Mechanism proposed for the tumor-inhibitory activity of squalene, based on its known strong inhibitory activity of HMG-CoA reductase activity. While found in epidemiological studies of breast and pancreatic cancer in several Mediterranean populations, olive oil was associated with a small decreased risk or no increased risk of cancer [16].

4.2 The most effective part of olive tree for breast/ colorectal cancer.

Over centuries, olive oil was used as a cosmetic and pharmacological agent. Olive oil is mainly comprised of monounsaturated fatty acids [23], with minor components including various phenolics [12]. On the other hand, olive oil, especially extra virgin, contains smaller amounts of tyrosol and hydroxytyrosol phenols. Also contains plenty of secoiridoids and lignans compounds. Both olives and olive oil contain essential amounts of other compounds considered anticancer agents (like squalene and terpenoids) [24].

12 out of the 14 included studies in this systematic review were about the effect of olive oil (virgin, extra-virgin) on cancer. One study was about the relationship between olive leaf and cancer. The reminder study was about the effect of both olive oil and olive leaf on cancer.

4.2.1 Olive oil

Over years, several studies have related olive oil ingestion to a low incidence of several diseases, like breast cancer. In united states of America, the USDA lists four grades of olive oil, which were established in 1948, based on acidity, absence of defects, odor and flavor: 1-Extra-virgin olive oil, 2-virgin olive oil, 3-Lampante Virgin Olive Oil , and 4-olive oil. According to the International Olive Oil Council, virgin olive oil extracted mechanically, without and chemical intervention. Extra-virgin olive oil comes only from virgin oil productions and contains no more than 0.8 percent acidity. Extra-virgin olive oil should be cold-pressed, that means no heat was used during processing over a certain temperature. However, Extra-virgin olive oils are fragile, that is high temperatures and even light can lead to their deterioration. It is worth to mention that labels “pure olive oil” and just plain old “olive oil” indicate a blend of refined and virgin oil [25].

The main active components of olive oil are monounsaturated lipids (mainly oleic acid), phenolic constituents (like hydroxytyrosol (HT), tyrosol and oleuropein (OL)) and squalene [6]. During olive oil storage, hydrolysis of oleuropein (OL), results in the formation of hydroxytyrosol (HT), tyrosol and ethanol. HT and OL phenols are considered potent antioxidants [4, 26]. Furthermore, hydroxytyrosol and tyrosol are two of the major phenols present in virgin olive oils play a significant roles in human health [5].

A research was conducted to evaluate and quantify the effect of consumption of olive oil, margarine, and a range of food groups on the risk of breast cancer. Data from 820 women with breast cancer and 1548 control women from the study base were used. It was found that increased olive oil consumption was associated with significantly reduced breast cancer risk, and the olive oil association was apparently concentrated among postmenopausal women, but the relevant interaction term was not statistically significant. It was concluded that olive oil consumption may reduce the risk of breast cancer [27].

Menendez et al (2005) investigated the effect of Oleic acid (OA) on the growth of breast cancer cells. They demonstrated that OA suppressed Her-2/neu overexpression, which, in turn, interacted synergistically with anti-Her-2/neu immunotherapy by promoting cell death of breast cancer cells. This offered a molecular mechanism by which individual fatty acids may regulate the malignant behavior of breast cancer cells [28].

Experimental studies in animals had clearly shown an influence of dietary lipids on breast cancer. While cohort studies have generated conflicting results, case-control analyses and prospective studies had shown that high fat intake was a risk of breast cancer. For more than 20 years, the experimental model of breast cancer used female Sprague-Dawley rat [6]. Moreover, Terzuoli et al (2016) studied the effects and mechanism of 2-(3,4-dihydroxyphenil) ethanol (or hydroxytyrosol, HT), a polyphenol from extra virgin olive oil, on the epidermal growth factor receptor (EGFR) expression in colon tumour cells. They revealed a new mechanism for HT's antitumour effects [29].

4.2.2 Olive leaf

The two studies that discussed the role of olive leaf, were review type. They found inhibitory and protective effects of olive leaf on cancer cells. Oleuropein, that gives bitter taste for unprocessed olives, is the most prevalent phenolic component in olive leaves, seed, pulp and peel of unripe olives (come up to 14% of the dry weight) [13]. However, the highest quantity is found in olive leaves [11]. Oleuropein, which inhibits cell growth, has direct anti-tumor effects and has been considered as a class of anti-cancer compounds [4, 26]. This is consistent with an experimental in vitro study which found that Olive-leaf crude extracts inhibit cell proliferation of human breast adenocarcinoma (MCF-7). The dominant compound of the extracts was oleuropein; phenols and flavonoids were identified too. These phytochemicals demonstrated strong antioxidant potency and inhibited cancer at low micromolar concentrations [30].

4.3 Conclusions

Based on results of clinical, experimental, and epidemiological studies that included in this systematic review, the role of olive was mainly protective, and the most effective part is the olive oil, even fried olive oil . Therefore, it is highly recommended to use virgin olive oil in daily diets. Furthermore, studies on olive leaf were mainly experimental; and there was strong evidence from cell models that olive polyphenols, mainly oleuropein, inhibit the progression and development of cancer. Hence, extracts of olive leaf can be used in cancer treatment.

Conflicts of Interest

The author declares no conflict of interest**.**

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