COMMENTARY

Olive: Fruit of Peace Against Cancer

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Abstract

The olive has a history almost as long as that of Western civilization and has been looked upon as a sign of hope, peace, and sacredness. Olive oil, extracted from the olive, is the principal source of dietary fat in the Mediterranean basin. The composition differs from that of other dietary fats in that olive oil is rich in monounsaturated fatty acids. Even other than as a source of monounsaturated fats, olive oil has own unique effects. Accumulating evidence suggests that olive oil may have beneficial health effects, especially when it comes to reducing risk factors for coronary heart diseases, preventing cancer, and modifying immune and inflammatory responses. However, evidence remains limited, definitive conclusions are difficult to draw, and there remains a significant need for further studies, particularly prospective cohort and well-designed, controlled intervention studies.

In this manuscript, the beneficial health effects of olive oil are reviewed, with particular attention paid to cancer prevention and immune functions.

Key Words: Olives - olive oil - antioxidants - immune functions - cancer prevention

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Introduction

The olive has a history almost as long as that of Western civilization and its cultivation dates back to biblical times. It has been celebrated and referenced in cultural works of all the ancient societies in Western Asia and has been looked upon as a sign of hope, peace, and sacredness by different cultures down to the present. The universal symbol of the United Nations is the Earth flanked by a wreath of crossed olive branches.

The olive is native to the Mediterranean region, tropical and central Asia, and various parts of Africa. It is also grown commercially in California, Australia, and South Africa.The olive tree (*Olea europaea*) belongs to the family *Oleaceae*. It is an evergreen long-living species with a life expectancy of 500 years. It may grow as high as 50 feet with a spread of about 30 feet. The leaves are feather-shaped and gray-green in color, growing in pairs opposite each other, and replace themselves every 2 or 3 years. The olive fruit is a green drupe, and it becomes generally blackish-purple when fully ripe. The cultivars vary considerably in size, shape, oil content, and flavor.

Olive Oil Production: Sun-ripened olives are harvested, sorted, and chosen for their quality. Once picked, they are washed to remove all impurities. The first step in extraction is the crushing of the olives to form a pomace. Oil from the pomace is separated using hydraulic press plates or by applying a continuous horizontal centrifuge.

Types of Olive Oil: Olive oil may be consumed in its natural unrefined state or in a refined state. High-quality, natural, unrefined olive oil is known as *extra-virgin olive oil*. Processing of low-quality oil yields *refined virgin olive oil*. If residual pomace or husk is processed with the use of organic solvents, the oil yielded is called refined husk olive oil. Refining causes a decrease in the phenolic component of olive oil and a partial decrease in the oil's antioxidant effects (Owen et al., 2000).

Beneficial Health Effects of Olive Oil

Across cultures, there are many different dietary patterns, some of which promote health while others increase the risk of chronic diseases. From ancient times to the present, olives and olive oil have been used for many medicinal purposes. In the Mediterranean basin, olive oil has thus found application as a treatment for ear aches, constipation, stomach aches, gastritis, and gastroduodonal ulcers.

Epidemiologic studies have documented lower death rates and higher life expectancy in Mediterranean populations in comparison with Scandinavian countries, the United Kingdom, and the United States (Trichopoulou et al., 2000; Trichopoulou and Vasilopoulou, 2000; Willett,

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1994). Diet is thought to play an important role in this difference and many studies have shown that the Mediterranean diet has significant protective effects, especially against cancer and coronary heart disease, which are leading causes of about 50% of all deaths in Western countries (Keys et al., 1981; Gerber, 1994). The traditional Mediterranean diet has 8 main components: a high monounsaturated-to-saturated fat ratio; moderate ethanol consumption; high consumption of legumes; high consumption of cereals; high consumption of fruits; high consumption of vegetables; low consumption of meat and meat products; and moderate consumption of milk and dairy products (Trichopoulou et al., 2000).

The principal source of dietary fat in the Mediterranean diet is olive oil. Olive oil differs significantly in composition from other dietary lipids in that it is very high in monounsaturated fatty acids and also has many antioxidative properties. The major antioxidants in olive oil are phenolic compounds and squalene (Stark and Madar, 2002; Trichopoulou, 1995; Hill and Giacosa, 1992).

Fatty Acid Composition of Olive Oil: The fatty acid composition of olive oil differs from that of other seed oils. Olive oil contains high amounts of monounsaturated fatty acids (MUFAs), especially oleic acid, whereas seed oils are rich in polyunsaturated linoleic acid, which is especially prone to oxidation and is a precursor of arachidonic acid (Moreno, 2003). The therapeutic properties of olive oil are often attributed to its high levels of MUFAs, mainly oleic acid. However, new evidence suggests that oleic acid may not be as important as other components, especially phenolic compounds and squalene (Stark and Madar, 2002). Time of harvest and crop year may affect the fatty acid composition of olive oil (Beltran et al., 2004).

Phenolic Compounds in Olive Oil: Olive oil is a source of at least 30 phenolic compounds. The major ones are simple phenols (hydroxytyrosol and tyrosol), secoiridoids (oleuropein), and lignans. The phenolic compounds in olive oil are strong antioxidants and radical scavengers (Owen et al., 2000; Owen, 2000; Tuck and Hayball, 2002). It has been reported that the radical scavenging activity of some of these compounds is even higher than that of the most-used antioxidants (Briante et al., 2003; Mateos et al., 2003).

In the literature, reports of the total phenolic content of olive oil vary widely, although values are generally between 50 and 500 mg/kg (Montedero et al., 1992; Montedero et al., 1993; Owen et al., 2000). The total phenolic content of olive varies depending on the cultivar, climate, and degree of ripeness of the olive (Amiot et al., 1989; Ryan et al., 1999; Bouaziz et al., 2004).

Similar to total phenolic content, reports for the oleuropein, hydroxytyrosol, and tyrosol contents of olive oil also vary in the literature. We believe that in future epidemiologic studies, both the nature and source of the olive oil consumed should be differentiated (Owen et al., 2000; Tuck and Hayball, 2002). Production and storage techniques, and the methods used to determine the phenolic content of the olive oil, also may have a role in this variation (Montedero et al., 1992; Brenes et al., 1999; Tuck and Hayball, 2002).

Squalene Content of Olive Oil: Olive oil contains large amounts of squalene, significantly higher than some other vegetable oils, including corn, peanut, and sunflower oils (Owen et al., 2000). Tumor-inhibiting effects of squalene have been reported (Rao et al., 1998; Murokoshi et al., 1992), and it has been concluded that squalene is an important component of the cancer-preventing effects of olive oil (Newmark, 1999).

Olive Oil, Cancer and Immune Functions

The physiologic function of the immune system is to recognize and destroy clones of transformed cells before they grow into tumors and to kill tumors after they have formed. The principal mechanism of tumor immunity is through the killing of tumor cells by CD8+ cytotoxic T-lymphocytes (CTLs). Natural killer (NK) cells kill many types of tumor cells, especially cells that have reduced class I major histocompatibility complex expression and can escape lysis by CTLs (Abbas, 2000). Different studies show that olive oil may have a potential role in lowering the risk of malignant neoplasms, such as mammary gland and colon tumors. Kossoy and coworkers have shown that, in rats, feeding mothers the 15% olive-oil diet has a cancer-inhibiting role in offspring, predominantly via changes at the cellular level such as increasing the number of CD8+ CTL (Kossoy et al., 2001).

In patients treated with long-term cisplatin, genetic damage can be observed during chemotherapy or for years afterward owing to its clastogenic potential. Evengelista and coworkers have shown that, in rats, pretreatment with a single dose of olive, extra virgin olive, and canola oils causes a statistically significant decrease in the number of chromosomal aberrations and abnormal metaphases induced by cisplatin, when compared with rats treated with cisplatin alone. The authors suggest that a possible explanation for the anticlastogenic effects may be ascribed to the oil contents of these oils (Evangelista et al., 2004), especially hydrocarbons, sterols (β-sitosterol and tyrosol), and phenols. Phenolic compounds, in particular, behave as antioxidants. Mediterranean diets rich in olive oil supply 10-20 mg of phenols per day, which can be completely absorbed into systemic circulation following oral intake (Visioli et al., 2000).

Uncontrolled production of reactive oxygen species and arachidonic acid metabolites contributes to the pathogenesis of cancer (Floyd, 2000). Inflammatory cells infiltrating tumors are a major source of reactive oxygen species. In addition, the antioxidant effect of olive oil has antiinflammatory potential. These effects depend on β-sitosterol and tyrosol (Moreno, 2003). There is some evidence that the effects of olive oil on immune suppression

in animal studies are due to oleic acid rather than to trace elements or antioxidants (Miles and Calder, 1998). In contrast to animal studies, consumption by healthy human subjects of a diet rich in oleic acid does not appear to bring about general supression of immune cell functions (Yaqoop et al., 1998). This topic clearly deserves further exploration.

Olive Oil and Prevention of Specific Cancers

The incidence of, and mortality from, several major cancers, including those of the breast, colon, ovary, stomach, endometrium, and prostate, are lower in Mediterranean countries than they are in countries of northern Europe or North America. Epidemiologic factors have been suggested as having an important role in this discrepancy and among these factors, diet has special importance (Trichopoulou, 2000; Trichopoulou and Vasilopoulou, 2000; Willett, 1994). Fat-related cancers at sites in the colon, breast, prostate, corpus uteri, and ovary are good examples of the diet-cancer relationship. Not only the amount of dietary fat intake, but the type and composition of fatty acids and the ratio of n-6 PUFAs to n-3 PUFAs are also important (Tokudome et al., 2000). Olive oil is the main source of total fat intake and is a key component of the Mediterranean diet. Olive oil consists of triglycerides, with a high content of monounsaturated fatty acids, especially oleic acid (Moreno, 2003).

It has been estimated that if the populations of highly developed Western countries could shift to the traditional healthy Mediterranean diet, up to 25% of colorectal cancers (CRC), ~15% of breast cancers, and ~10% of prostate, pancreas, and endometrial cancers could be prevented (Trichopoulou, 2000).

Colon Cancer: CRC rates have been relatively low in the Mediterranean area compared with most other Western countries (Levi et al., 1994). It has been suggested that dietary fat (not only the amount of fat but also the type of fat consumed) may be important in colorectal carcinogenesis (Woutersen et al., 1998; Braga et al., 1998). Many studies have been conducted to elucidate this relationship.

In one of these studies, national levels of dietary factors, with particular reference to olive oil, from 28 countries from 4 continents (including southern and northern Europe, Australia, Canada, and the United States) were analyzed and compared. It was reported that 76% of the intercountry variation in CRC incidence rates could be explained by 3 significant dietary factors: consumption of meat, fish, and olive oil. Olive oil consumption was negatively associated with the risk of colorectal cancer, while meat and fish consumption were positively associated with the risk of colorectal cancer (Stoneham et al., 2000).

Braga and colleagues, in a case control study between 1992 and 1996 in 6 Italian areas, investigated the relationship between various fats and CRC risk. Dietary habits of 1953 patients with incident, histologically confirmed CRC, and 4154 controls with no history of cancer were investigated. They concluded that fats do not appear to increase the risk of CRC, and there is little evidence for a differential effect by fat types. If such a differential effect exists, it is minor and could favor olive oil rather than other fat types (Braga et al., 1998). In another case control study, Benito and coworkers, using a 99-item food frequency questionnaire, reported no statistically significant association between olive oil intake and colorectal cancer. The study population was made up of 286 cases of CRC, 295 population controls, and 203 hospital controls (Benito et al., 1991).

In an experimental study, Llor and colleagues studied the role of different fats in apoptosis induction, cell proliferation, and differentiation. They supplemented Caco-2 and HT-29 colorectal cancer cells with different fats. Supplementation with fish oil or olive oil resulted in an induction of apoptosis and cell differentiation (Llor et al., 2003). Although data from the literature are thus not conclusive, they appear to favor olive oil consumption.

Breast Cancer: Age-adjusted breast cancer incidence varies strikingly around the world, and incidence rates of breast cancer in Mediterranean countries are relatively low compared with those of most other Western countries (Cohen and Wynder, 1990).

In offspring of migrants moving from countries with low incidence of breast cancer to countries with high incidence, breast cancer incidence increases and becomes close to the rate of the new country (Ziegler et al., 1993). These data suggest the importance of environmental and lifestyle influences in the etiology of breast cancer. Among these environmental factors, diet has a significant role. It has been shown that breast cancer incidence and mortality around the world are highly correlated with per capita fat consumption (Carrol, 1975; Armstrong and Doll, 1975). The association between breast cancer and dietary fat has been widely investigated; however, the results remain controversial. Smith-Warner and coworkers, pooling data from 8 prospective studies, reported that dietary fat intake is not associated with breast cancer (Smith-Warner et al., 2001). In another meta-analysis of 12 case control studies, Howe and colleagues reported a consistent, statistically significant, positive association between breast cancer risk and saturated fat intake in postmenopausal women (Howe et al., 1990). However, the populations in these studies did not habitually consume olive oil; their consumption of fat was predominantly from meat and dairy sources.

The relation between olive oil and breast cancer can best be studied in the Mediterranean basin where the substantial proportion of dietary fat is consumed as olive oil. Studies in this region have shown an inverse association between breast cancer and olive oil consumption (Lipworth et al., 1997). Three such case control studies have been conducted in Italy. In one of these studies, La Vecchia and coworkers looked at a population of 2564 women hospitalized with histologically confirmed breast cancer and 2588 matched hospital controls, and showed an inverse association between olive oil intake and breast cancer risk. The odds ratio (OR) per unit (30 g) increase in olive oil consumption was 0.89

(95% confidence interval, 0.81-0.99, p=0.03) (La Vecchia et al., 1995). In another study by Toniolo and coworkers, 250 women with confirmed breast cancer and 499 age-matched population controls were administered questionaires, and a negative relation between the intake of olive oil and risk of breast cancer was found; however, the results were not statistically significant (Toniolo et al., 1989). In one very recent study, 8984 female volunteers were recruited from 1987 to 1992. All of them completed a semiquantitative food frequency questionnaire. With an average follow-up of 9.5 years, 207 incident cases of breast cancer were analyzed to identify major dietary patterns. At the end of follow-up, it was suggested that a diet rich in raw vegetables and olive oil protects against breast cancer (Sieri et al., 2004).

Two further case control studies have been conducted in Spain. In one of them, Martin-Moreno and colleagues found total fat intake to not be associated with breast cancer. While there was a negative association observed for monounsaturated fatty acids and oleic acid, the trend was not statistically significant. However, a higher consumption of olive oil was significantly related to a lower risk of breast cancer (Martin-Moreno et al., 1994). In the other study from Spain, it was reported that consumption of fruits, vegetables, and fish was significantly lower in breast cancer cases. A lower intake of monounsaturated fatty acids also was shown in the breast cancer group when compared with the controls (Landa et al., 1994).

In a study conducted in Greece, Trichopoulou and coworkers studied the effect of consumption of olive oil, margarine, and a range of food groups on the risk of breast cancer. They observed that olive oil consumption was associated with a significantly reduced risk of breast cancer (Trichopoulou et al., 1995).

All of the above-mentioned studies point to a preventative role of olive oil consumption in breast cancer. However, the results are far from conclusive, and there is a great need for future research.

Ovarian Cancer: In a case control study conducted between 1992 and 1999 in Italy, Basetti and colleagues analyzed data from 1031 cases of epithelial ovarian cancer and 2411 hospital controls with acute nonmalignant and nongynecological conditions. The subjects usual diet was investigated and a reduced risk of ovarian cancer was observed for those whose intake included olive and other vegetable oils (for olive oil, the OR was 0.68; 95% CI: 0.50-0.93). No significant associations were observed for mixed seed oils, butter, or margarine (Bosetti et al., 2002).

In another study conducted in Greece, Tzonou and coworkers reported an inverse relation between monounsaturated fat intake (mostly from olive oil) and risk for ovarian cancer (OR = 0.80; 95% CI: 0.65-0.99 for a 1-SD increase in consumption). Cases in this study were composed of 189 women with epithelial ovarian cancer and 200 hospital visitors (controls) (Tzonou et al., 1993).

Again, the evidence is limited, and the results should be taken as no more than an indication of a possible effect.

Lung Cancer: Fortes and coworkers, in a case control study conducted in Rome during 1993 to 1996, examined the relation between food consumption and lung cancer risk. Using a self-administered food frequency questionnaire, data were obtained from 342 cases of primary lung cancer and 292 hospital controls. It was found that exclusive use of olive oil had a protective effect for lung cancer (OR = 0.67; 95% CI: 0.45-0.99). A protective effect also was found for high consumption of carrots, tomatoes, white meat, and regular consumption of sage. The authors concluded that some food items typical to the Mediterranean diet are associated with a decreased risk of lung cancer (Fortes et al., 2003).

Conclusions

Dietary recommendations for cancer prevention have been made by several health authorities. According to guidelines of the the American Cancer Society, obesity should be avoided; intake of fruits, vegetables, and whole grain cereals should be greatly increased; total dietary fat should be reduced; alcohol consumption should be limited; and intake of animal fats should be decreased. The traditional Mediterranean diet is an excellent example of such a diet. Mediterranean dietary habits still exist, but a significant departure from the traditional Mediterranean diet has been reported, especially in younger generations (Tur et al., 2004). During the last few decades, decreased consumption of carbohydrates, stable intake of protein, and increased intake of fats and oils have been reported worldwide (Tokudome et al., 2000).

Olive oil is the principal source of total fat intake in the Mediterranean diet. Long recognized for its beneficial effect on human health, current scientific studies suggest that olive oil is one of the reasons for the lower rate of cancer among people in the Mediterranean region. Scientific evidence, derived primarily from epidemiologic studies as well as from animal and in vitro experiments, indicates that regular consumption of olive oil is inversely associated with cancer at different sites. Data are limited, however, and conclusions are difficult to make. Further studies are needed, particularly prospective cohort studies and well-designed, controlled intervention studies. Still, the findings concerning the role of olive oil in cancer prevention are encouraging.

Which component (or components) of olive oil is responsible for its protective effect remains questionable. MUFAs seem to play a central role, but other components including phenolic compounds, squalene, tocopherols, and other micronutrients may contribute to olive oil's cancer-protective effect.

Traditionally, olive oil production has been concentrated in the Mediterranean basin. Mediterranean countries alone account for about 90% of all worldwide production. The main producers are also the main consumers. The annual per capita olive oil consumption is around 10 kg in Mediterranean countries, 0.45 kg in the United States, and

0.02 kg in Japan (Filik and Ozyilkan, 2003).

The relationship between olive oil and cancer risk not only provides a target for future clinical studies seeking to find ways to prevent carcinogenesis, but it offers a basis for developing new strategies for public health planners and governments, especially in countries with relatively low olive oil consumption. Finally, we can truly say that the olive, the fruit of peace, deserves especial consideration for increasingly use in the fight against cancer in the future.

References

Abbas A, Lichtman HA, Probers J: Cellular and molecular immunology. 4th ed. New York WB. Saunders 2000.

Amiot MJ, Fleuriet A, Macheix JJ (1989). Accumulation of oleuropein derivatives during olive maturation. *Phytochemistry*, **28**, 67-9.

Amiot MJ, Fleuriet A, Macheix JJ (1996). Importance and evaluation of phenolic compounds in olive during growth and maturation. *J Agric Food Chem*, **34**, 823-6.

Armstrong B, Doll R (1975). Environmental factors and cancer incidence and mortality in different countries, with special reference to dietary practices. *Int J Cancer*, **15**, 617-31.

Beltran G, Del Rio C, Sanchez S, Martinez L (2004). Influence of harvest date and crop yield on the fatty acid composition of virgin olive oils from cv. Picual. *J Agric Food Chem*, **52**, 3434-40.

Benito E, Stiggelbout A, Bosch FX, et al (1991). Nutritional factors in colorectal cancer risk: a case control study in Majorca. 1. Dietary factors. *Int J Cancer*, **49**, 161-7.

Braga C, La Vecchia C, Franceschi S, et al (1998). Olive oil, other seasoning fats, and the risk v of colorectal carcinoma. *Cancer*, **82**, 448-53.

Brenes M, Garcia A, Garcia P, et al (1999). Phenolic compounds in Spanish olive oils. *J Agric Food Chem*, **47**, 3535-40.

Bosetti C, Negri E, Franceschi S, et al (2002). Olive oil, seed oils and other added fats in relation to ovarian cancer. *Cancer Causes Control*, **13**, 465-70.

Briante R, Febbraio F, Nucci R (2003). Antioxidant properties of low molecular weight phenols present in the mediterranean diet. *J Agric Food Chem*, **51**, 6975-81.

Bouaziz M, Chamkha M, Sayadi S (2004). Comparative study on phenolic content and antioxidant activity during maturation of the olive cultivar Chemlali from Tunisia. *J Agric Food Chem*, **25**, 5476-81.

Carroll KK (1975). Experimental evidence of dietary factors and hormone-dependent cancers. *Cancer Res*, **35**, 3374-83.

Cohen LA, Wynder EI (1990). Do dietary monounsaturated fatty acids play a protective role in carcinogenesis and cardiovascular disease? *Med Hypotheses*, **31**, 83-9.

Evangelista CM, Antunes LM, Francescato HD, Bianchi ML (2004). Effects of the olive, extra virgin olive and canola oils on cisplatin-induced clastogenesis in Wistar rats. *Food Chem Toxicol*, **42**, 1291-7.

Filik L, Ozyilkan O (2003). Olive oil consumption and cancer risk. *Eur J Clin Nutr*, **57**, 191.

Floyd RA (1990). Role of oxygen free radicals in carcinogenesis and brain ischemia. *FASEB J*, **4**, 2587-97.

Fortes C, Forastiere F, Farchi S, et al (2003). The protective effect of the Mediterranean diet on lung cancer. *Nutr Cancer*, **46**, 30-7.

Gerber M. Olive oil and cancer (1994). In Epidemilogy of diet and cancer (eds. Hill MJ, Giacosa A, Caygill CPG); Chichester: Ellis Horwood, pp. 263-75.

Hill M, Giacosa A (1992). The Mediterranean diet. *Eur J Cancer Prev*, **1**, 339-40.

Howe GR, Hirohata T, Hislop TG, et al (1990). Dietary factors and risk of breast cancer: combined analysis of 12 case-control studies. *J Natl Cancer Inst*, **82**, 561-9.

Keys A, Aravanis C, Van Buchem H, et al (1981). The diet and the all-causes death rate in the Seven Countries Study. *Lancet*, **2**, 58-61.

Kossoy G, Madar Z, Ben-Hur H, et al (2001). Transplacental effect of a 15% olive-oil diet on functional activity of immune components in the spleen and colon tumors of rat offspring. *Oncol Rep*, **8**, 1045-9.

La Vecchia C, Negri E, Franceschi S, et al (1995). Olive oil, other dietary fats, and the risk of breast cancer (Italy). *Cancer Causes Control*, **6**, 545-50.

Landa MC, Frago N, Tres A (1994). Diet and the risk of breast cancer in Spain. *Eur J Cancer Prev*, **3**, 313-20.

Levi F, Lucchini F, La Vecchia C (1994). Worldwide patterns of cancer mortality, 1985-89. *Eur J Cancer Prev*, **3**, 109-43.

Llor X, Pons E, Roca A, et al (2003). The effects of fish oil, olive oil, oleic acid and linoleic acid on colorectal neoplastic processes. *Clin Nutr*, **22**, 71-9.

Lipworth L, Martinez ME, Angell J, et al (1997). Olive oil and human cancer: An assessment of the evidence. *Preventive Medicine*, **26**, 181-90.

Martin-Moreno JM, Willett WC, Gorgojo L, et al (1994). Dietary fat, olive oil intake and breast cancer risk. *Int J Cancer*, **58**, 774-80.

Mateos R, Dominguez MM, Espartero JL, Cert A (2003). Antioxidant effect of phenolic compounds, alpha-tocopherol, and other minor components in virgin olive oil. *J Agric Food Chem*, **51**, 7170-5.

Miles EA, Calder PC (1998). Modulation of immune function by dietary fatty acids. *Proc Nutr Soc*, **57**, 277-92.

Montedoro G, Servilli M, Baldioli M, Miniati E (1992). Simple and hydrolysable phenolic compounds in virgin olive oil. 2.Initial characterisation of hydrolysable fraction. *J Agric Food Chem*, **40**, 1577-80.

Montedoro G, Servilli M, Miniati E (1992). Simple and hydrolysable phenolic compounds in virgin olive oil.1. Their extraction, seperation, and quantitative and semiquantitative evaluation by HPLC. *J Agric Food Chem*, **40**, 1571-6.

Montedoro G, Servilli M, Baldioli M, et al (1993). Simple and hydrolysable phenolic compounds in virgin olive oil. 3. Spectroscopic characterisation of secoiridoid derivatives. *J Agric Food Chem*, **41**, 2228-34.

Moreno Juan J (2003). Effect of olive oil minor components on oxidative stress and arachidonic acid mobilization and metabolism by macrpohages RAW 264.7. *Free Radic Biol Med*, **35**, 1773-1081.

Murakoshi M, Nishino H, Tokuda H, et al (1992). Inhibition by squalene of the tumor-promoting activity of 12-O-tetradecanoylphorbol-13-acetate in mouse-skin carcinogenesis. *Int J Cancer*, **52**, 950-2.

Newmark HL (1999). Squalene, olive oil, and cancer risk. Rewiev and hypothesis. *Ann NY Acad Sci*, 889, 193-203.

Owen RW, Giacosa A, Hull WE, et al (2000). Olive-oil consumption and health: the possible role of antioxidants. *Lancet Oncol*, **1**, 107-12.

Owen RW, Giacosa A, Hull WE, et al (2000). The antioxidant /

anticancer potential of phenolic compounds isolated from olive oil. *Eur J Cancer*, **36**, 1235-47.
Owen RW, Mier W, Giacosa A, et al (2000). Phenolic compounds and squalene in olive oils: the concentration and antioxidant potential of total phenols, simple phenols, secoiridoids, lignans and squalene. *Food Chem Toxicol*, **38**, 647-59.
Rao CV, Newmark HL, Reddy BS (1998). Chemopreventive effect of squalene on colon cancer. *Carcinogenesis*, **19**, 287-90.
Ryan D, Robards K, Lavee S (1999). Changes in phenolic content of olive during maturation. *Int J Food Sci Tech*, **34**, 265-74.
Sieri S, Krogh V, Pala V, et al (2004). Dietary patterns and risk of breast cancer in the ORDET cohort. *Cancer Epidemiol Biomarkers Prev*, **13**, 567-72.
Stark AH, Madar Z (2002). Olive oil as a functional food: Epidemiology and nutritional approaches. *Nutr Rev*, **60**, 170-6.
Stoneham M, Goldacre M, Seagroatt V, Gill L (2000). Olive oil, diet and colorectal cancer: an ecological study and a hypothesis. *J Epidemiol Community Health*, **54**, 756-60.
Smith-Warner SA, Spiegelman D, Adami HO, et al (2001). Types of dietary fat and breast cancer: a pooled analysis of cohort studies. *Int J Cancer*, **92**, 767-74.
Tokudome S, Nagaya T, Okuyama H, et al (2000). Japanese versus Mediterranean diets and cancer. *Asian Pac J Cancer Prev*, **1**, 61-6.
Toniolo P, Riboli E, Protta F, et al (1989). Calorie-providing nutrients and risk of breast cancer. *J Natl Cancer Inst*, **81**, 278-86.
Trichopoulou A, Lagiou P, Kuper H, Trichopoulos D (2000). Cancer and Mediterranean dietary traditions. *Cancer Epidemiol Biomarkers Prev*, **9**, 869-73.
Trichopoulou A (1995). Olive oil and breast cancer. *Cancer Causes Control*, **6**, 475-6.
Trichopoulou A, Vasilopoulou E (2000). Mediterranean diet and longevity. *Br J Nutr*, **84**, S205-9.
Tuck KL, Hayball PJ (2002). Major phenolic compounds in olive oil: metabolism and health effects. *J Nutr Biochem*, **13**, 636-44.
Tur JA, Romaguera D, Pons A (2004). Food consumption patterns in a mediterranean region: does the mediterranean diet still exist? *Ann Nutr Metab*, **48**,193-201.
Tzonou A, Hsieh CC, Polychronopoulou A, et al (1993). Diet and ovarian cancer: a case control study in Greece. *Int J Cancer*, **55**, 411-4.
Visioli F, Galli C, Bornet F, et al (2000). Olive oil phenolics are dose-dependently absorbed in humans. *FEBS Lett*, **468**, 159-60.
Willett WC (1994). Diet and health: what should we eat? *Science*, **264**, 532-7.
Woutersen RA, Appel MJ, van Garderen-Hoetmer A, Wijnands MV (1999). Dietary fat and carcinogenesis. *Mutat Res*, **443**, 111-27.
Yaqoob P, Knapper JA, Webb DH, et al (1998). Effect of olive oil on immune function in middle-aged men. *Am J Clin Nutr*, **67**, 129-35.
Ziegler RG, Hoover RN, Pike MC, et al (1993). Migration patterns and breast cancer risk in Asian-American women. *J Natl Cancer Inst*, **85**, 1819-27.