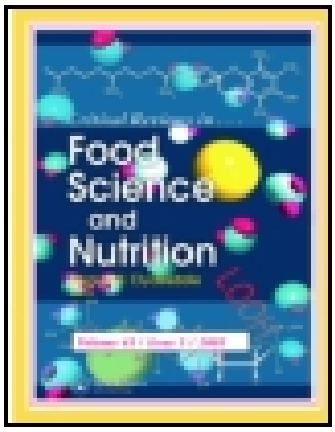

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The Anti-cancer and Anti-obesity Effects of Mediterranean Diet

Hiu Yee Kwan[a], Xiaojuan Chao[a], Tao Su[a], Xiuqiong Fu[a], Anfernee Kai Wing Tse[a], Wang Fun Fong[a] & Zhi-Ling Yu[a]

[a] Centre for Cancer and Inflammation Research, School of Chinese Medicine, Hong Kong Baptist University, Kowloon Tong, Hong Kong, China.

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Hiu Yee Kwan*, Xiaojuan Chao, Tao Su, Xiuqiong Fu, Anfernee Kai Wing Tse, Wang Fun Fong, Zhi-Ling Yu*

Centre for Cancer and Inflammation Research, School of Chinese Medicine, Hong Kong Baptist University, Kowloon Tong, Hong Kong, China.

Key Words: Mediterranean diet, Obesity, Cancer, Nutrition, Olive oil, Polyphenols

*To whom correspondence should be addressed:

Dr. Hiu Yee Kwan

Email: hykwan@hkbu.edu.hk

Dr. Zhi-Ling Yu

Email: zlyu@hkbu.edu.hk

Abstract

Cancers have been the leading cause of death worldwide and the prevalence of obesity is also increasing in these few decades. Interestingly, there is a direct association between cancer and obesity. Each year, more than 90000 cancer deaths are caused by obesity or overweight. The dietary pattern in Crete, referred as the traditional Mediterranean diet, is believed to confer Crete people the low mortality rates from cancers. Nevertheless, the anti-obesity effect of the Mediterranean diet is less studied. Given the causal relationship between obesity and cancer, the anti-obesity effect of traditional Mediterranean diet might contribute to its anti-cancer effects. In this regard, we will critically review the anti-cancer and anti-obesity effects of this diet and its dietary factors. The possible mechanisms underlying these effects will also be discussed.

Introduction

Cancer is currently one of the most important public health issues. World Health Organization (WHO) reported that 14% of global deaths were resulted from malignant neoplasm, and the incidence is expected to be 18 % in 2030 (Tyrovolas and Panaquitakos, 2010). On the other hand, the worldwide obesity is nearly doubled since 1980; more than 1.4 billion adults and 40 million children are overweight. In general, obesity is defined as excess accumulation of adipose tissue (Khandekar et al., 2011). Based on WHO definition, people with body mass index (BMI) $\geqq$ 30 are classified as obese, people with BMI $\geqq$ 25 are classified as overweight; however, different countries might have different modified cut off points.

Obesity has a profound influence on cancer risk (Pischon et al., 2008; Calle and Thun, 2004). Ample evidence demonstrates a positive correlation between excess body weight and an increased risk of cancers of the breast, colon, endometrium, gallbladder, adenocarcinoma of the oesophagus, kidney and pancreas (Key TJ et al., 2004). More than 90000 yearly cancer deaths are thought to be caused by obesity or overweight; and the incidence of obesity-related cancer death is estimated to be 14 % to 20 % (Calle and Thun, 2004).

Nowadays, people tend to have high energy intake but low energy expenditure. They consume foods rich in saturated fats, particularly n-6 polyunsaturated fatty acids (PUFAs) and trans-fatty acids; they do not have enough carbohydrate and fiber intakes (Simopoulos, 2004). These dietary patterns might be the underlying rationale explains the rising cancer incidences and the soaring obesity rates.

A particular food consumption pattern in about 16 countries bordering the Mediterranean Sea, described as Mediterranean diet (MD), has been widely studied for its anti-cancer effects, and to a less extend, its anti-obesity effect. In fact, MD is only a term describing the general dietary pattern in these countries. A close examination reveals that the dietary patterns in these countries actually vary nowadays. Italian diet includes high consumption of pasta; Greece diet includes high consumption of fish (Gallus et al., 2004). Even in the same country, the dietary patterns may also be different. The average consumptions of cereals, fruit and vegetables are higher in southern Italy; while milk and dairy products are higher in northern Italy (Gallus et al., 2004). The diet in Crete represents the traditional diet of Greece prior to 1960, which mimics the traditional MD. Crete's diet has a large variety of vegetables, fruit and nuts; it is also rich in whole grains and fatty fish but low consumption of meat and dairy products (de Lorgeril and

Salen, 2008). Olive oil is the main fat source (Alarcón de la Lastra et al., 2001) which is rich in monounsaturated fatty acids (MUFAs). Moderate alcohol drinking particularly the red wine is usually included in the diet.

Among populations around the Mediterranean regions, Crete has the best health status and the lowest morbidity and mortality rates from cancers (Kafatos A et al., 2000). It is believed that the Crete diet, referred as traditional MD, confers the Crete people these advantages. Indeed, beside the anti-cancer effects, MD may also possess anti-obesity effects.

In this study, we critically review the effectiveness of Crete diet (traditional MD) and its dietary factors in reducing cancer risks. Given the causal relationship between obesity and cancer, we will also summarize the anti-obesity effect of the diet. The possible mechanisms underlying these anti-cancer and anti-obesity effects will be discussed.

Cancer is a chronic inflammation

Cancer can be considered as a chronic inflammation. The link between chronic inflammation and cancer development was first noticed over 100 years ago by Rudolph Virchow when he observed

an abundance of leukocytes in neoplastic tissue (Balkwill and Mantovani, 2001). Indeed, in the tumor microenvironment, there are epithelial cells, fibroblasts, mast cells and cells of the innate and adaptive immune system that favor a proinflammatory and pro-tumorigenic environment (Ishigami et al., 2000; Ribatti et al., 2003; Leek et al., 1999). Tumor-associated macrophage (TAM) also plays a key role in the tumor environment (Pollard, 2004), it helps to promote tissue invasion (Coussens et al., 2000), angiogenesis (Murdoch et al., 2008) and metastasis (Qian et al., 2011). Besides these immune cells, cancer cells can produce tumor necrosis factor α (TNF α) (Lin and Karin, 2007; Harvey et al., 2011). TNF α activates NFκβ and the subsequent gene expressions which regulate many inflammatory signaling pathways and promote cancer development (Lin and Karin, 2007; Harvey et al., 2011). Cyclooxygenase 2 (COX2) is also overexpressed in many cancer types (Koki et al., 2002), which is critical for the production of eicosanoids such as prostaglandins and leukotrienes.

Traditional MD reduces cancer risks

Historically, incidence of overall cancer was lower in Mediterranean countries compared to northern European countries, UK and US (Trichopoulou et al., 2000). Cancer causes almost three times as many deaths proportionally in USA as in Crete (Simopoulos, 2004). Many studies have

demonstrated the beneficial effects of traditional MD in reducing cancer risks (Table 1). Early in 1958, the Seven Countries Study was conducted with samples randomly selected from cohorts in US, Italy, Japan, the Netherland, Greece, Finland and the former Yogoslavia (Keys et al., 1985). This study has already demonstrated the beneficial effects of traditional MD on health. In 1992, a case-control study held in Italy also suggested that traditional MD reduced risk for cancers of the upper aero-digestive tract (Bosetti et al., 2003). In similar years, the prostate, lung, colorectal and ovarian cancer screen trial (PLCO) in US revealed that traditional MD adherence reduced risk for colorectal cancer (Dixon et al., 2007). Studies done by The National Institute of Health-AARP diet (Kontou et al., 2011) and European prospective investigation into cancer and nutrition (EPIC) (Benetou et al., 2008), respectively, also suggested an inverse association between traditional MD and cancer risks. In developed countries such as US, it is estimated that up to 25 % of the incidence of colorectal carcinoma, 15 % of the incidence of breast cancer, 10 % of the incidence of prostate, pancreatic and endometrial cancer can be prevented if those people adhered to traditional MD (Trichopoulou et al., 2000). The greater the adherence to traditional MD, the lower the cancer mortality (Mitrou et al.,2007; Benetou et al., 2008). High adherence to traditional MD is associated with 22-25% reduction in breast cancer risk (Wu et al., 2009; Murtaugh et al., 2008) and 21-28% reduction in colorectal cancer risk (Reedy et al., 2008;

Dixon et al., 2007). Nevertheless, the cancer protective effects of traditional MD vary according to the population's characteristic and status such as smoking (Mitrou et al., 2007; Buckland et al., 2010), age group (Fung et al., 2006; Buckland et al., 2010), premenopausal or postenopausal status (Fung et al., 2006; Dalvi et al., 2007), gender (Benetou et al., 2008; Reedy et al., 2008; Dixon et al., 2007) and BMI status (Mitrou et al., 2007).

Dietary factors in the traditional MD reduce cancer risks

Polyphenols

In the traditional MD, many foods or dietary factors might have anti-cancer properties. Among all dietary factors, polyphenols gain the greatest attraction. Polyphenols are commonly found in fruits such as grapes, blueberries, strawberries, raspberries, citrus fruits; vegetables such as legumes and onion; whole grains such as cereals, bread and rye; fat such as olive oil and beverage such as tea and red wine. There are over 5000 polyphenolic compounds present in these fruits, vegetables and beverages of plant origin. Polyphenols can be divided into several groups according to the number of phenol rings that they contain and to the structural elements that join these rings. The main groups of polyphenols are flavonoids, phenolic acids, phenolic alcohol, stilbenes and lignans. All phenolic groups have antioxidant properties because of their chemical

structures (Knekt et al., 1997; Le Marchand L et al., 2000). Studies showed that polyphenols help to reduce risk of lung cancer (Knekt et al., 1997; Le Marchand et al., 2000). They also reduce inflammatory angiogenesis in cultured endothelial cells; inhibit expressions of matrix metalloproteinase 9 and COX2 (Curran and Murray, 1999).

Flavonoids are the most abundant polyphenol in traditional MD. They possess 15 carbons, with 2 aromatic rings (ring A and B) joined by a linear three-carbon chain usually forming a closed pyran ring (ring C). Flavonoids are further subdivided into classes according to the oxidation state of the central pyran ring. These subclasses are flavonols, flavones, flavanones, isoflavones, anthocyanidins and flavanols such as catechins and proanthocyanidins. Flavonoids have been shown to be antioxidant, antimutagenic and antiproliferative *in vitro* (Pelucchi et al., 2009). It is interesting that a high consumption of flavonoids is only associated with a reduced risk of breast cancer (Bosetti et al., 2005; Peterson et al., 2003), ovarian cancer (Rossi et al., 2008b), renal cell carcinoma (Bosetti et al., 2007), colorectal carcinoma and tumors of stomach and esophagus (Zamora-Ros et al., 2010). However, studies on prostate cancer (Bosetti et al., 2006) found no association with any of the flavonoids analyzed. The underlying rationales account for the differential effects of flavonoids on these cancers await further investigation.

Fiber

Fiber increases the bulk of stool and decreases its transit time in the colon. Therefore, it decreases the time the colonic epithelial cells exposed to potential fecal carcinogens (Williams and Hord, 2005). Besides, dietary fiber also reduces glycemic load, improves insulin resistance and favorably influences insulin-like growth factor-1 (IGF-1) which promotes the process of carcinogenesis at various site (Yu and Rohan, 2000). Epidemiologic studies show a strong inverse relationship between dietary fiber intake and colon cancer (Peters et al., 2003; Bingham et al., 2003). Increase dietary fiber to 20 g a day from average current intake would reduce the rate of colorectal carcinogenesis by 40% (Bingham and Riboli, 2004). Whole grain food is high in fiber content, and it has been related to a reduced risk of colorectal carcinoma (Gallus et al., 2004). Besides, frequent consumption of whole grains significantly decreases the risk of many cancers including those of the upper aero-digestive tract, stomach, liver, breast, ovary, bladder and kidney (Chatenoud et al., 1999; Chatenoud et al., 1998). Nevertheless, fiber may offset carcinogenic effect of N-nitroso compounds by acting as a nitrite scavengers (Lewin et al., 2006). The bacterial in gut can ferment fiber to short chain fatty acids such as butyrate which may promote colonic cell differentiation and induce apoptosis in normal cells (Key et al., 2004).

Whole grain foods with high contents of dietary fiber also help to reduce glycemic load (Yu and

Rohan, 2000). Refined grain intake with high glycaemic load is associated with increased risk of stomach, colorectal, upper aero-digestive tract and thyroid cancers (Augustin et al., 2001; Augustin et al., 2003a; Augustin et al., 2003b; Chatenoud et al., 1999; Franceschi et al., 2001).

Carotenoids

There are more than 500 carotenoids, found in all yellow-orange-red fruits and vegetables. Carotenoids show an inverse relation with breast cancer risk (Negri et al., al., 1996). Besides, low intake or low plasma level of B-carotene is at risk of developing lung cancer (Gerber, 2003).

Lycopene

Lycopene can be found in tomato and it is inversely related to several digestive tract neoplasm but not to breast and prostate cancer (Bosetti et al., 2004; La Vechia, 2002a; La Vecchia and Bosetti C, 2006).

Vitamin C

A negative association is found between gastric cancer risk and plasma concentrations of vitamin C and carotenoids (Buckland et al., 2010; Gerber, 2003). The proposed mechanism of action of

vitamin C in cancer prevention and treatment includes stimulation of immune system, alteration of carcinogen metabolism and enhancement of collagen synthesis for tumor encapsulation (Ullah et al., 2012). Interestingly, vitamin E is also an antioxidant. However, results obtained from observational studies cannot conclusively report a beneficial role of vitamin E in reducing cancer risks (Gerber, 2003).

Folate

Folate intake is inversely related to cancers of large bowel, breast, the upper aerodigestrive tract (Negri et al., 2000) and prostate (Pelucchi et al., 2005a; Pelucchi et al., 2005b); and the protective role of dietary folate is consistent across strata of age (La Vecchia et al., 2002b). However, no study supports the protective role of folate in ovarian carcinogenesis (Pelucchi et al., 2005b).

Olive oil

Olive oil is the main fat source in traditional MD. The virgin olive oil is produced from the first and second processing of the olive oil by the cold-pressing method, where no chemicals and only a small amount of heat is applied (Cicerale et al., 2009). The virgin olive oil is composed of a

glycerol fraction (making up 90-99% of the olive fruit) and a non-glycerol or unsaponifiable fraction (making up 0.4-5% of the olive fruit) (Tripoli et al., 2005). Olive oil does not compete with the desaturation and elongation of linolenic acid (LNA) or with the incorporation of n-3 polyunsaturated fatty acid (PUFAs) into the cell membrane phospholipids; therefore, it provides an additional benefit to the functions of n-3 PUFAs (Simopoulos et al., 2004).

Besides its own beneficial properties, olive oil also facilitates the consumption of large quantities of vegetable and legumes in the form of raw salads and cooked food (Trichopoulou et al., 2000) and therefore further enhances these nutrient contents.

Oleic acid in olive oil

The healthful properties of virgin olive oil are attributed to a high proportion of MUFAs, namely oleic acid (18:1n-9), which represents 70-80% of the fatty acids present in virgin olive oil (Tripoli et al., 2005; Waterman and Lockwood, 2007). Oleic acid has antioxidant properties (Owen et al., 2000), it helps to make cells less susceptible to oxidation by reducing the formation of proinflammatory molecules (Owen et al., 2004). Besides, studies found that oleic acid downregulated COX2 expressions which play an important role in colorectal cancer

development (Waterman and Lockwood, 2007). Oleic acid also induces apoptosis in HT-29 cells (Waterman and Lockwood, 2007), downregulates Her-2 oncogene expression in 20% of breast carcinoma (Menendez et al., 2005). Other study also showed that oleic acid suppressed oncogene HER2 which plays a key role in the etiology, invasive progression and metastasis in several human cancers (Menendez and Lupu, 2006).

However, a study showed that oleic acid had no association with colorectal cancer as opposed to the inverse relationship found for n-3 PUFAs (Theodoratou et al., 2007). The French component of the EPIC documented an intake of cis-MUFA appears to be unrelated to breast cancer risk (Chajes et al., 2008). Several seed oil rich in MUFA have been demonstrated to be ineffective in beneficially altering chronic disease risk factors (Aguilera et al., 2004; Harper et al., 2006). Therefore, other components in olive oil may also attribute to the beneficial effects of virgin olive oil in reducing cancer risks.

Phenolic contents in olive oil

Phenolic fraction of virgin olive oil has generated much interest regarding its health promoting properties (Cicerale et al., 2009). The total phenolic content in virgin olive oil has been reported

to be in the range of 196-500mg/kg (Owen et al., 2000). Moreover, these phenolics are highly bioavailable (Cicerale et al., 2009). At least 36 structurally distinct phenolics that have been identified in virgin olive oil but not all phenolics are present in every virgin oil and there is variation in the phenolic concentration between virgin olive oils, because of an array of production factors (Cicerale et al., 2009).

Olive oil phenolics have been found to decrease arachidonic acid release and arachidonic acid metabolite synthesis; both are involved in the inflammatory process (Moreno, 2003). Phenolics extracted from virgin olive oil have been demonstrated to decrease the invasiveness of colon cancer cells (Gill et al., 2005), inhibit cell proliferation in human promyelocytic HL60 luekemia cells (Fabiani et al., 2006). The main phenolic compounds in virgin olive oil are secoiridoid derivatives of 2-(3,4-dihydroxyphenyl)ethanol (hydroxytyrosol) which positively affect human hepatoma cells antioxidant defense system and favor cell integrity (Goya et al., 2007). Hydroxytyrosol (3,4-dihydroxyphenylethanol) (DOPET) is the major o-diphenol of virgin olive oil, it presents in both a free and esterified form (Manna et al., 2002). DOPET also possess anti-proliferative effect in HL-60 cells (Della Ragione et al., 2000). Another phenolic compound is oleuropein aglycone which is found to inhibit the growth of MCF-7 and SKRB3 breast cancer

cells, and reduce expression of HER2 oncogene which plays a role in malignant transformation, tumorigenesis and metastasis (Menendez et al., 2007).

Squalene in olive oil

Squalene accounts for 0.7% in olive oil (Newmark, 1997) and is responsible for the lower incidence of skin cancer as animal studies showed that topical squalene had an inhibitory action on chemically-induced skin carcinomas (Newmark, 1997; Waterman, 2007)

Lignans in olive oil

Lignans inhibits the development of cutaneous tumors, mammary, colonic, pulmonary cancers (Tripoli et al., 2005). The antitumoral effect of lignans is based on both their antioxidant activities (Prasade, 1997; Owen et al., 000) and their antiviral activities (Tripoli et al., 2005).

Olive leaf crude extract

Study also found that the olive leaf crude extract inhibited cell proliferation of human breast adenocarcinoma (MCF-7), human urinary bladder carcinoma (Goulas et al., 2009). The identified dominant compounds of the extract are oleuropein, phenols and flavonoids (Goulas et al., 2009).

Essential fatty acids (EFAs)

Linoleic acid (LA) and linolenic acid (LNA) are the two EFAs in our body. LA is an n-6 PUFA while LNA is an n-3 PUFA. LA can be found in eggs, poultry, vegetable oil and whole grain bread; LNA in flaxseed, linseed, soy oil, walnuts and leafy green vegetable.

EFAs are the precursors for the synthesis of eicosanoids such as prostaglandins and leukotrienes. Eicosanoids are the main mediators of inflammation. EFAs are converted to prostaglandins by COXs or to leukotrienes by lipoxygenases. In general, arachidonic acid derived from LA will generate pro-inflammatory 2-series prostanoids and 4-series leukotrienes; whereas LNA-derived eicosapentaenoic acid will generate anti-inflammatory n-3 prostanoids and 5 series leukotrienes. Therefore, these eicosanoids have opposite effects on inflammation and therefore opposite effects on cancer progression. It has been suggested that n-6 PUFAs increase size and number of tumor, n-3 PUFAs decrease both (Cave, 1991). Indeed, n-6 PUFAs stimulate prostate cancer progression and n-3 PUFAs inhibit it (Ritch et al., 2007). The principal EFA in the US diet is LA, which may account for the high incidence of cancers compared to regions adhered to traditional MD.

The n-3 PUFAs from dietary intake will incorporate into cell membrane at the expense of arachidonic acid concentration and its metabolites, therefore suppress biosynthesis of proinflammatory eicosanoids (Pauwels, 2011; Grimble, 2001). Besides, n-3 PUFAs also induce apoptosis (Schley et al., 2007) and inhibit angiogenesis in cancer cells (Rose, 1999). Supplementation of n-3 PUFAs has been reported to suppress inflammation and diminish oxidative stress (Yaqoob, 2007; Kenar et al., 2008). Indeed, the n-3 PUFAs supplementation for breast cancer chemo-prevention has been strongly supported by both epidemiologic and experimental studies (Simopoulos, 2006). Other studies also demonstrate that n-3 PUFAs are inversely related to both colon and rectal cancer risks (Hall et al., 2008). The protective effects against breast, colon and prostate cancers are suggested to be mediated by suppression of neoplastic transformation, inhibition of cell growth, induction of apoptosis and anti-angiogenicity through inhibition of eicosanoid productions from n-6 PUFAs (Simopoulos, 2006). It is also found that n-3 PUFAs downregulated the over-expressed COX2 in colon cancer (Chen and Istfan, 2000). Interestingly, biopsies of adipose breast tissue in women with invasive non-metastatic breast carcinoma or benign breast disease show no association between breast cancer and saturated fatty acids, monounsaturated fatty acid and long chain n-6 PUFAs (Klein et

al., 2000); however, LNA levels in these biopsies show an inverse association with the risk of breast cancer (Klein et al., 2000).

Although n-3 PUFAs, rather than n-6 PUFAs, possess a better protective role in reducing cancer risk, we cannot eliminate n-6 PUFAs from diet as they are EFAs. There are always competition and opposition of these two classes of EFAs in the body. Indeed, many studies show that ratio of the n-6 to n-3 PUFAs, rather than the absolute level of either class, is more critical in cancer prevention (Cowing and Saker, 2001; Simopoulos, 2006).

Red wine

Moderate red wine drinking is defined as one drink (5 oz) per day for women and two for men. Red wine is rich in phenolic compound which exert anti-inflammatory and antioxidant actions. Highly tanned red wine can contain up to 3 g of total polyphenols per liter and the amount of catechin and epicatechin derivatives, including oligomeric procyanidins can even reach ~800 mg per liter (Giacosa et al., 2013). Piceatannol is one of the polyphenols present in grapes and wine. Experimental study shows that piceatannol has cytotoxic effect on hepatoma (Kita et al., 2012), implying its protective role in liver cancer.

Quercetin is one of the flavonols abundantly present in red wine and is known to possess potent antiproliferative effects against various malignant cells. Quercetin induces apoptosis *via* the mitochondrial pathway in human gastric cancer cells by increasing caspase-3 expression (Wang et al., 2012). Our laboratory also showed that quercetin possessed anti-melanoma effects (unpublished data).

Resveratrol (trans-3,5,4'-trihydroxystilbene) is another antioxidant found in red wine (Simopoulos, 2004). Resveratrol in red wine originates from skin and seeds of grapes, its antioxidant activity is attributed to the inhibition of TNF α-activated NFκβ signaling, leading to a reduced biosynthesis of proinflammatory prostaglandinds such as prostaglandin E2 (Subbaramaiah et al., 1998; Shankar et al., 2007; Nakata et al., 2012). More importantly, effect of resveratrol on COX2 expression is cell specific, it does not suppress COX2 expression in human umibilical vein endothelial cells (Nakata et al., 2012). Although red wine has many antioxidant components, the protective role of red wine in reducing cancer risks is still debatable as inconsistent findings have been reported on its role in non-hodgkin lymphoma, thyroid cancer, renal cell carcinoma and breast cancer (Morton et al., 2005; Lee et al., 2007; Mack et al., 2003;

Lachenmeier et al., 2012). Other studies even show that low to moderate consumption may increase risk of cancers including cancers of colorectal, liver, breast, oral cavity, pharynx, esophagus and larynx (Allen et al., 2009). These inconsistent findings imply that the protective role of antioxidants in red wine may be outweighed by the alcohol content in the wine. It is known that the effects of alcohol consumption on cardiovascular disease always show a J-shaped curve (Thompson, 2013), similarly, the J-shaped curve may also apply to the effect of alcohol in red wine on cancers. A balance between alcohol consumption and polyphenols / antioxidants intakes from red wine, non-misclassification of drinking patterns and clear definition of "low to moderate drinking" may be critical in studying the effect of red wine on reducing cancer risks.

Association between cancer and obesity

There is an association between cancer and obesity, and it may be due to convergence of pathway involving adipokines, inflammation and insulin resistance (Khandekar et al., 2011) (Figure 1).

Obesity is associated with chronic state of inflammation. The obesity-associated inflammation is thought to be one of the most important factors connecting obesity to cancer (Khandekar et al., 2011). Indeed, it has reported that obesity-associated inflammation contributed to cancer

progression in several organs. Adipocytes can trans-differentiate into macrophage (Charriere et al., 2003), and produce inflammatory cytokines such as TNF α, interleukin-6 (IL-6), IL-1B and monocyte chemoattractant protein such as monocyte chemotactic protein-1 (Harvey et al., 2011). More importantly, the cytokines that are secreted by adipose tissue will further recruit macrophages to the site and hence further increases the levels of the inflammatory mediators (Harvey et al., 2011) and promote cancers grow (Khandekar et al., 2011). Nevertheless, there are also reports demonstrating that production of these cytokines from adipose tissue is actually from monocytes (Weisberg et al., 2003) and the immune cells that infiltrated the adipose tissue (Ruan et al., 2003).

Adipokines released from adipocytes affect cancer progression. Leptin can modulate immune function, cytokine production, angiogenesis and carcinogenesis (Lord et al., 1998; Somasundar et al., 2003a, 2003b). The effects of leptin on cancer cell proliferation involve activation of mitogen-activated protein kinases (MAPK) (Hardwick et al., 2001; Choi et al., 2005). Leptin also signals through a transmembrane receptor (OBR) which contains intracellular tyrosine that can mediate downstream signaling *via* extracellular signal-regulated kinases (ERK) and signal transducer and activator of transcription 3 (STAT 3) pathways (Banks et al., 2000). *In vitro*

studies shows leptin has proliferative effect on many cancer types including cancers of esophageal, breast, ovary, prostate and colon cancers (Somasundar et al., 2003; Hardwick et al., 2001; Onuma et al., 2003; Choi et al., 2005). Epidemiology study reveals an association between leptin levels and prostate cancer risk in Scandinavian men (Stattin et al., 2001). In Japan, study on women with colorectal cancer indicates that leptin is associated with increased risk (Tamakoshi et al., 2005). However, other results show no association between leptin level and increased breast cancer in a regression analysis in Massachusetts (Mantzoros et al., 1999). In Greek, after adjustment for BMI, men leptin levels are not correlated with prostate cancer incidence (Lagiou et al., 1998). Adiponectin is another well-known adipokines. Adiponectin inhibits prostate and colon cancer growth (Kim et al., 2010). It increases c-Jun N-terminal kinase (JNK) phosphorylation, decreases mammalian target of rapamycin (mTOR) phosphorylation and induces apoptosis in hepatocellular carcinoma cells (Sharma et al., 2010). Epidemiology studies show an inverse relationship between systemic adiponectin concentration and cancer risk in colon, prostate, gastric, endometrial, and renal cancers in multiple case-control studies (Tian et al., 2007; Wei et al., 2005; Sher et al., 2008; Dal Maso et al., 2004; Cust et al., 2007). However, a prospective study shows that adiponectin levels are not predictive of endometrial cancer risk (Soliman et al., 2011).

The association between obesity and cancer also lie in the fact that obese people usually have elevated levels of circulating insulin (Khandekar J et al., 2011) due to some degree of insulin resistance (Samuel et al., 2010)**.** And it seems that the increased insulin can promote cancer grow in the absence of leptin (Khandekar et al., 2011). Insulin promotes cancer development *via* binding to insulin receptor and initiating signal transduction in ERK and phosphatidylinositide 3-kinases (PI3K) pathways (Renehane et al., 2008). Insulin also reduces insulin-like growth factor (IGF)-binding protein level, thereby increasing the amount of bioavailable IGF-1 that interact with IGF-1 receptor (IGF-1R) (Harvey et al., 2011). IGF-1 binds to IGF-1R and activates downstream ERK and PI3K which modulate transcription factors that control gene expression related to cancer development (Harvey et al., 2011). Besides, IGF-1 can also transactivate leptin receptor, results in a synergistic effect on breast cancer cell proliferation (Saxena et al., 2008). Indeed, levels of IGF-1 are often elevated in obese individuals (Calle and Thun, 2004; Frystyk, 2004).

The anti-obesity effect of traditional MD

Dated back to 1960s, obesity and overweight were certainly not prevalence in Crete or basins

around Mediterranean regions. Therefore, the anti-obesity effect of traditional MD may have been overlooked. Given a large number of cancer deaths might be caused by obesity or overweight, it is reasonable to postulate that the anti-obesity effect of the traditional MD might contribute to its anti-cancer effect.

Indeed, there are many studies showing an inverse association between traditional MD and adiposity indexes (Schroder et al., 2004; Panagiotakos et al., 2006; Romaguera et al., 200; Schroder et al., 2010; Buckland et al., 2008). Clinical trials also support this association (Shai et al., 2008; McManus et al., 2001; Nordamann et al., 2011). In EPIC-PANACEA project (European Prospective Investigation into Cancer and Nutrition – Physical Activity, nutrition, Alcohol consumption, cessation of smoking, eating out of home and obesity project) with a total of 373803 individuals aged range from 25 to 70, it is found that individual with a high adherence to traditional MD pattern showed a 5-year weight loss of 0.16 kg and were 10% less likely to develop overweight or obesity than individual with a low adherence to the traditional MD pattern (Romaguera et al., 2010). Similar conclusions are drawn with the Spanish cohort in the study of the European Prospective Investigation into Cancer and Nutrition (EPIC-Spain) (Mendez et al., 2006). Up to 2008, there were 21 epidemiological studies assessing the relationship between

obesity and traditional MD; and no studies reported that traditional MD significantly increased body weights (Buckland et al., 2008). Instead, more than half of these studies provided evidence that the adherence to traditional MD was associated with less overweight or obesity, or even promoted weight loss (Buckland et al., 2008). Nevertheless, a few other studies also demonstrated that traditional MD was not improving the BMI or waist-to-hip ratio (WHR) in both sexes (Rossi et al., 2008a; Trichopoulou et al., 2005). A summary of the anti-obesity effects of traditional MD is shown in Table 2.

The dietary explanation for the anti-obesity effect of traditional MD is based on the high consumption of plant-based food that provides a large quantity of fiber, low energy density and low glycemic load (Willett and Leibel, 2002). The low meat content of the traditional MD certainly accounts for the positive effect of the diet against weight gain (Romaguera et al., 2010). Compared with high saturated fats, monounsaturated fats in traditional MD help to improve glucose metabolism (Due et al., 2008), increase postprandial fat oxidation, enhance diet-induced thermogenesis and therefore increase the overall daily energy expenditure (Soares et al., 2004; Piers et al., 2003). Dietary monounsaturated fats also promote healthy blood lipid profiles, mediate blood pressure and improve insulin sensitivity (Gillingham et al., 2011). All these

suggest monounsaturated fats in traditional MD ameliorate the risk of obesity.

Besides, other dietary factors which possess potential anti-obesity effects (Trigueros et al., 2013) can also be found in traditional MD such as n-3 PUFAs, phenolic compounds, soybeans and dietary fiber. Dietary antioxidants in traditional MD will also help to reduce risk of obesity (O'Keefe and Abuannadi, 2010). Moreover, consumption of traditional MD has been found to be positively associated with adiponectin levels (Reis et al., 2010).

Recently, it is also shown that resveratrol is a potential anti-obesity compound, it directly affects lipolysis and glucose transport in human fat cells (Gomez-Zoritas et al., 2013). In the experimental study, resveratrol facilitates isoprenaline stimulation and impairs insulin antilipolytic action in the human subcutaneous fat tissue; therefore impairs glucose uptake and decreases triglyceride assembly in these fat cells (Gomez-Zoritas et al., 2013). The overall effects are increased β-adrenergic-stimulated lipolysis and impaired lipogenesis; resulting in decreased fat cell sizes.

Although mounting evidence showing a positive correlation between obesity and an increased risk of cancers, and adherence to traditional MD helps to reduce weight gain, we do not have

enough epidemiological and clinical evidence suggesting the anti-obesity effect of traditional MD helps to anti-cancer. A proposed mechanism of action is suggested for the anti-cancer effects of traditional MD (Figure 2).

Difficulties in assessing the anti-cancer effect of traditional MD

Foods or dietary factors are not consumed in isolation, and their health effects are often synergistic (Kant, 2004). In the Greek cohort of EPIC (European prospective investigation into cancer and nutrition), it was found that traditional MD was significantly and inversely associated with cancer risk but the associations of the individual MD components with the cancer were all non-significant (Benetou et al., 2008). Therefore, the cancer protective effects of the traditional MD pattern may be stronger than that of an individual food or dietary factor.

There are many difficulties in assessing the anti-cancer effect of traditional MD. Cancer is not solely associated with diet or foods. Other factors may cause cancer such as genetic inheritance, geographic factors, exposure to carcinogens or some particular lifestyles. These risk factors may over- or under-estimate the anti-cancer effects of traditional MD. Indeed, the association between traditional MD adherence and cancer risk is stronger for smokers (Couto et al., 2011).

Conclusion

Diet can be an important factor affecting not only body weight but also risks of cancers. Adherence to the traditional MD appears to be effective in reducing both the weight gain and cancer risk. However, more investigations are definitely needed to suggest the correlation between adherences to traditional MD to reduce in weight gain and hence reduce in cancer risks in individuals.

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Table 1 Summary of dietary factors in traditional MD with reported anti-cancer effects

Chemical Group / Compound	Food Source	Mechanism of Action	Anti-cancer Property	Reference
Polyphenols	Olive oil Red wine	✧ Antioxidant ✧ Inhibited matrix metalloproteinase 9 (MMP9) and angiogenesis ✧ Reduced inflammatory	Reduced risk of lung cancer	Knekt et al., 1997; Le Marchand et al., 2000; Curran et al., 1990.
Flavonoids	Citric fruit e.g.orange Vegetable e.g. onions Beverages of plant origin Red wine	✧ Antioxidant ✧ Antimutagenic ✧ Antiproliferative	Reduced risk of breast cancer,	Bosetti et al., 2005; Peterson et al., 2003.
			Reduced risk of ovarian cancer	Rossi et al., 2008.
			Reduced risk of renal cell carcinoma	Bosetti et al., 2007.
			Reduced risk of tumors of stomach, esophagus, colorectal, breast, renal cell	Zamora-Ros et al., 2010.

			carcinoma, No relationship with lung, bladder, epithelial or other cancers No relationship with prostate cancer	Zamora-Ros et al., 2010. Bosetti et al., 2006.

Table 1 Summary of dietary factors in traditional MD with reported anti-cancer effects

(continued)

Chemical Group / Compound	Food Source	Mechanism of Action	Anti-cancer Property	Reference
Quercetin	Grapes, Red wine	✧ Changed the apoptotic protein expression e.g. decrease in Bcl-2/Bax ratio ✧ Increased expression of caspase-3 ✧ Induced apoptosis mediated via the	Antiproliferative effects against various malignant cells	Wang et al., 2012.

	mitochondrial pathway		

Table 1 Summary of dietary factors in traditional MD with reported anti-cancer effects

(continued)

Chemical Group / Compound	Food Source	Mechanism of Action	Anti-cancer Property	Reference
Vegetables			Decreased risk of epithelial cancer	Pelucchi et al., 2009; Gallus et al., 2004.
Fiber	Whole grain food Vegetables	✧ Reduced glycaemic load ✧ Improved insulin resistance, favorably influencing insulin-like growth factor I (IGF-1) which promoted carcinogenesis ✧ Increased the bulk of stool, decreased transit time that colonic epithelial cells exposed to potential fecal carcinogens ✧ Offset	Reduced risk of colon cancer in population at low risk of the diseases An increase dietary fiber to 20g a day from average current intake reduced the rate of colorectal cancer by 40%	Yu and Rohan, 2000; Peters et al., 2003; Bingham et al., 2003; Yu and Rohan, 2000; Bingham et al., 2004. Williams et al., 2005 Lewin et al.,

		carcinogenic effect of N-nitroso compounds by acting as a nitrite scavengers		2006
		✧ Bacterial in gut can ferment fiber to short chain fatty acids e.g. butyrate	Promote colonic cell differentiation and normal cell apoptosis	Key et al., 2004

Table 1 Summary of dietary factors in traditional MD with reported anti-cancer effects

(continued)

Chemical Group / Compound	Food Source	Mechanism of Action	Anti-cancer Property	Reference
Vitamin C	Fruit	✧ Antioxidant ✧ Stimulated immune system ✧ Altered carcinogen metabolism ✧ Enhanced collagen synthesis necessary for tumor encapsulation ✧ Interfered with cancer cell signaling	Reduced risk of digestive tract and laryngeal cancer	Pelucchi et al., 2009; Gerber, 2003.

				Negative association was found between plasma vitamin C concentration, vitamin E and carotenoid concentration and gastric cancer risk	Buckland et al., 2010.
Vitamin E		✧	Antioxidant	No conclusive relationship with cancers in observational studies	Gerber, 2003.
Carotenoids	Yellow-orange-red fruits Vegetables	✧	Antioxidant	Low intake or low plasma level of B-carotene were at risk of developing lung cancer Reduced risk of breast cancer	Gerber, 2003; Negri et al., 1996; La Vecchia et al., 2006.

Table 1 Summary of dietary factors in traditional MD with reported anti-cancer effects

(continued)

Chemical Group / Compound	Food Source	Mechanism of Action	Anti-cancer Property	Reference
Locypene	Tomato		Reduced risk of several digestive tract	Bosetti et al., 2004; La

				neoplasm	Vechia, 2002.
				No relationship with breast and prostate cancer	La Vecchia and Bosetti, 2006
Folate				Reduced risk of cancer in upper aerodigestive tract and large bowel Reduced risk of breast cancer Protective role on colorectal cancer across strata of age	Negri et al.,2000; Pelucchi et al.,2005; Pelucchi et al., 2009; La Vechia et al., 2002.
				No relationship with ovarian carcinogenesis	Pelucchi et al., 2005.
Selenium	Cereal Fish	✧ ✧	Antioxidant Co-factor of glutathione peroxidase	Reduce risk of prostate cancer	Helzlsouer et al., 2000; Yoshizawa et al.,1998.

Table 1 Summary of dietary factors in traditional MD with reported anti-cancer effects

(continued)

Chemical Group / Compound	Food Source	Mechanism of Action	Anti-cancer Property	Reference
Olive oil		✧ High in monounsaturated fatty acids e.g. oleic acid ✧ High levels of	Reduced risk of several cancers especially oral and pharyngeal cancer, upper aero	Pelucchi et al., 2009; Franceschi et al., 1999.

		squalene, vitamin E and phenolic compounds ✧ Antioxidant properties due to both oleic acid itself and to the presence of other antioxidants	digestive tract	
		✧ Induced apoptosis in large intestinal cancer cells ✧ Downregulated COX2 and Bcl2 expression in colorectal carcinogenesis	Inhibited colon cancer development	Kontou et al., 2011.
			Reduced risk of breast cancer	Lipworth et al., 1997.
	Facilitates the consumption of large quantities of vegetable and legumes in the form of raw salads and cooked food			

Table 1 Summary of dietary factors in traditional MD with reported anti-cancer effects

(continued)

Chemical	Food	Mechanism of Action	Anti-cancer	Reference

Group / Compound	Source		Property		
Oleic acid	Olive oil	✧	Made the cell less susceptible to oxidation by reducing the formation of proinflammatory molecules		
		✧	Suppressed oncogene HER2 which plays a key role in the etiology invasive progression and metastasis	Reduced risk of breast cancer	Menendez et al., 2006.
				No relationship with breast cancer risk	Chajes et al., 2008.
				No relationship with colorectal cancer	Theodoratou et al., 2007.

Table 1 Summary of dietary factors in traditional MD with reported anti-cancer effects

(continued)

Chemical Group / Compound	Food Source		Mechanism of Action	Anti-cancer Property	Reference
Alpha-linolenic acid	Fish Flaxseed	✧ ✧	Enhanced apoptosis Anti-angiogenesis	Reduced risk of colon and rectal	Hall et al., 2008.

(n-3 fatty acid)	Linseed Soy oil Walnuts Leafy green vegetable	✧ Suppressed biosynthesis of proinflammatory eicosanoids ✧ Diminished oxidative stress ✧ Suppressed neoplastic transformation ✧ Inhibited cell growth ✧ Enhanced apoptosis ✧ Anti-angiogenicity through inhibition of eicosanoids production from n-6 fatty acid	cancer Protective effects against breast, colon and prostate cancer Reduced risk of breast cancer	Simopoulos, 2004. Simopoulos, 2004.
		✧ Downregulated COX2 expression ✧ Induced apoptosis	Reduced risk of colorectal cancer No association was found between fatty acids (saturates, MUFA, long chain PUFA n-6 or n-3) and breast cancer	Chen and Istfan, 2000; Simopoulos, 2004.. Klein et al., 2000.

Table 1 Summary of dietary factors in traditional MD with reported anti-cancer effects

(continued)

Chemical Group / Compound	Food Source	Mechanism of Action	Anti-cancer Property	Reference
Resveratrol	Red wine	✧ Inhibited arachidonate metabolism ✧ Suppressed PGE2 synthesis ✧ Inhibited TNFα-activated NFκB signaling, ✧ Reduced biosynthesis of proinflammatory prostaglandins ✧ Reduced activity of COX2	Reduced risk of breast cancer	Nakata et al., 2012; Subbaramaiah et al., 1998; Shankar et al., 2007.
Piceatannol	Wine Grapes		Against hepatoma AH109A cells	Kita et al., 2012.
			Moderate red wine drinking does not help cut women's breast cancer risk	Lachenmeier and Rehm, 2012.
			"Mediterranean way of drinking", did not appreciable influence the overall risk of cancer	Giacosa et al., 2013.
			Low to moderate alcohol consumption may increase risk of certain cancers	Allen et al., 2009.

	(cancer of oral cavity, pharynx, esophagus, larynx, colorectum, liver, female breast)	
	No consistent findings on protective effect of wine on non-hodgkin lymphoma, thyroid cancer, renal cell carcinoma	Morton et al., 2005; Lee et al., 2007; Mack et al., 2003.

Table 2 Summary of the traditional MD with obesity risk

Traditional MD Association with Obesity Risk	Reference
Inversely associated with obesity risk	Beunza et al., 2010; Buckland et al., 2008; Gallus et al., 2006; Lassale et al., 2012; Martinez-Gonzalez et al., 2012; Mendez et al., 2006; Mendez et al., 2006; McManus et al., 2001; Nordamann et al., 2011; Sanchez-Villegas et al., 2006; Romaguera et al., 2010; Schroder et al., 2004; Panagiotakos et al., 2006; Romaguera et al., 2009; Schroder et al., 2010; Romaguera et al., 2010; Schroder et al., 2004; Shai et al., 2008
Not inversely associated with obesity risk	Trichopoulou et al., 2005; Rossi et al., 2007.

Figure Legends

Figure 1

Figure 1 Interplay between cancer and obesity

Figure 2 Potential pathways: Anti-cancer effects of traditional Mediterranean diet