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Giacosa, Attilio[a,b]; Barale, Roberto[c]; Bavaresco, Luigi[d]; Gatenby, Piers[l]; Gerbi, Vincenzo[e]; Janssens, Jaak[n]; Johnston, Belinda[m]; Kas, Koen[o]; La Vecchia, Carlo[f,g]; Mainguet, Paul[n]; Morazzoni, Paolo[h]; Negri, Eva[f]; Pelucchi, Claudio[f]; Pezzotti, Mario[i]; Rondanelli, Mariangela[j,k]

[a]Department of Surgery, University of Genoa, Genoa
[b]Department of Gastroenterology, Policlinico di Monza, Monza
[c]Department of Biology, University of Pisa, Pisa
[d]CRA-Research Centre for Viticulture, Conegliano
[e]Di Va PRA, Microbiology and Food Technology Sector, University of Turin, Turin
[f]Mario Negri Institute for Pharmacological Research
[g]Department of Occupational Health, University of Milan
[h]Indena, Milan
[i]Department of Biotechnology, University of Verona, Verona
[j]Department of Applied Health Science, University of Pavia
[k]ASP (Azienda di Servizi alla Persona) of Pavia, Pavia, Italy
[l]Division of Surgery and Interventional Science, Faculty of Medical Science, University College London, London
[m]Lady Sobell Gastrointestinal Unit, Wexham Park Hospital, Slough, UK
[n]European Cancer Prevention Organization, Hasselt
[o]InBioVeritas, Schilde, Belgium
Correspondence to Attilio Giacosa, MD, PhD, Department of Gastroenterology, Policlinico di Monza, Via Amati 111, Monza 20900, Italy Tel: +30 329 926 2099; fax: +39 010 587 341; e-mail: attilio.giacosa@policlinicodimonza.it

Keywords: alcohol, cancer, Mediterranean diet, polyphenols, prevention, wine

Abstract

In the coming years, European death rates because of cancer will further decline, but the overall number of cases will increase, mostly as a consequence of the ageing of the population. The target for cancer prevention in Europe will remain a healthy diet and control of obesity in addition to a decrease in smoking. A healthy diet model in European countries is the traditional Mediterranean diet, which is based on abundant and variable plant foods, high consumption of cereals, olive oil as the main (added) fat, low intake of (red) meat and moderate consumption of wine. The Mediterranean diet is associated with a reduced risk of cardiovascular disease and cancer. The biological mechanisms for cancer prevention associated with the Mediterranean diet have been related to the favourable effect of a balanced ratio of omega 6 and omega 3 essential fatty acids and high amounts of fibre, antioxidants and polyphenols found in fruit, vegetables, olive oil and wine. The Mediterranean diet also involves a 'Mediterranean way of drinking', that is, regular, moderate consumption of wine mainly with food. This pattern of drinking increases longevity, reduces the risk of cardiovascular disease and does not appreciably influence the overall risk of cancer. However, heavy alcohol drinking is associated with digestive, upper respiratory tract, liver and breast cancers; therefore, avoidance or restriction of alcohol consumption to two drinks/day in men and one drink/day in women is a global public health priority.

Introduction

Cancer incidence and trends in Europe Although more than 40% of cancer deaths can be prevented, cancer represents the second most important cause of death and morbidity in Europe, with more than three million new cases and 1.7 million deaths each year. On a global scale, cancer accounted for 7.4 million deaths (around 13% of the total) in 2004. Around one-quarter of all cancer cases occurred in Europe, which accounts for only one-eighth of the world population. Tobacco and excessive alcohol consumption cause about

one-third of the total cancer burden, with precise figures varying from country to country. If the consequences of an inappropri- ate diet, obesity and insufficient physical activity are included, the percentage of cancers because of an unhealthy lifestyle increased to 40%. Lung, colon and breast cancer result in the highest number of cancer deaths each year in Europe and tobacco use is the single most important risk factor for cancer (www.euro.who.int/en/what-we-do/health-topics/noncommunicable-diseases/cancer/facts-and-figures, 2010). Not only does Europe have a wide range in incidence of all common cancers, it also has a wide range in dietary patterns, environmental exposures and social behaviour. Europe offers an ideal 'laboratory' for the formulation and testing of hypotheses on the causation of human cancers. The highest incidence of cancer in Europe is found for colon and rectum, breast, lung (with the highest mortality), prostate, stomach (high mortality), bladder (some problems with differ- ences in coding in different countries), pancreas (very high mortality), head and neck, kidney and non-Hodgkin lymphoma (Ferlay et al., 2010). Lung, cervix and stomach cancer are more common in South and Central Europe. Scandinavia appears to have incidences similar to the UK and Denmark. Colorectal cancer is stable/increasing because of changing nutritional habits and obesity in countries with a traditionally low incidence and mortal- ity. Melanomas, prostate, testicular, female lung and breast cancer incidences are increasing (the latter two are because of increased smoking and changing repro- ductive patterns, respectively). Larynx, ovarian and bladder cancer are stable or decreasing. Consistent decreases have been observed for gastric, cervical and male lung cancer because of improved food preservation, improved personal hygiene and Helicobacter pylori eradi- cation, screening programmes and decreased male smoking, respectively (Karim-Kos et al., 2008; Ferlay et al., 2010). The latter two are the major factors influencing the observed trends of death because of cancer. In the coming years, European cancer death rates may decline further, but the overall number of cases will increase, mostly as a consequence of increasing smoking among women, increasing obesity and ageing (La Vecchia, 2011). Therefore, the next target for cancer prevention in Europe will involve the adoption of a healthy diet and control of obesity in addition to a decrease in smoking habits.

Obesity and cancer

Ample evidence has been collected to show a positive correlation between excess body weight and an increased risk of cancers of the breast (postmenopausal), colon, endometrium, gallbladder, adenocarcinoma of the oeso- phagus, gastric cardia, kidney and pancreas.

Adipose tissue is an active endocrine organ. The mechanisms by which adipose tissue may influence the risk of cancer are production of sex steroid hormones (e.g. oestrogen, androgen), effects on insulin sensitivity and the production of insulin-like growth factors, actions on other hormones in adipose tissue (e.g. leptin, adiponec- tin) and increases in oxidative stress and chronic low- grade inflammation that affect the body's immune response (Van Kruijsdijk et al., 2009). In obesity, increased release from adipose tissue of free fatty acids, tumour- necrosis factor-a and resistin, and reduced release of adiponectin lead to the development of insulin resistance and compensatory, chronic hyperinsulinaemia. Increased insulin levels, in turn, lead to reduced liver synthesis and blood levels of insulin-like growth factor-binding protein 1 (IGFBP1) and probably also reduce IGFBP1 synthesis locally in other tissues. Increased fasting levels of insulin in the plasma are also generally associated with reduced levels of IGFBP2 in the blood. This results in increased levels of bioavailable IGF1. Insulin and IGF1 signal through the insulin receptors and the IGF1 receptor, respectively, promote cellular proliferation and inhibit apoptosis in many tissue types. These effects might contribute to cancerogenesis (Calle and Kaaks, 2004). Moreover, adipose tissue produces the enzymes aroma- tase and 17b-hydroxysteroid dehydrogenase. Therefore, in obese individuals, there is typically an increased conversion of the androgens

D4-androstenedione (D4A) and testosterone (T) into the oestrogens oestrone (E1) and oestradiol (E2), respectively, by aromatase. 17b-Hydroxysteroid dehydrogenase converts the less biologically active hormones D4A and E1 into the more active hormones T and E2, respectively. In parallel, obesity leads to hyperinsulinaemia, which in turn causes a reduction in the hepatic synthesis and circulating levels of sex-hormone-binding globulin. The combined effect of increased formation of oestrone and testosterone, along with reduced levels of sex-hormone-binding globulin, leads to an increase in the bioavailable (free) fractions of E2 and T that can diffuse to target cells, where they bind to oestrogen and androgen receptors. The effects of sex steroids' binding to their receptors can vary depending on the tissue types, but in some tissues (e.g. breast epithelium and endometrium), they promote cellular proliferation and inhibit apoptosis (Calle and Kaaks, 2004).
Obesity is the second (to tobacco) leading risk factor for cancer in North America. Further, it has important public health implications for chronic diseases such as type 2 diabetes, orthopaedic malformations, hypertension, car- diovascular diseases and cancer. Future research should focus on how the risk of cancer is affected by successful and sustained weight loss.

Mediterranean diet and cancer

A healthy diet model in European countries is the traditional Mediterranean diet, which is based on abundant and variable plant foods, high consumption of cereals, olive oil as the main (added) fat, low intake of (red) meat and moderate consumption of wine. A diet rich in fruit and vegetables protects against common epithelial cancers, including in particular, those of the digestive tract. The intake of whole-grain food has been consistently related to a reduced risk of colorectal cancer and other neoplasms (Aune et al., 2011). Several case–control studies have reported a favourable effect of fibres on colon and rectal cancers; in contrast, intake of refined grains has been associated with an increased risk of stomach, colorectal and upper digestive tract cancers in studies conducted in Mediterranean populations. Refined cereals and sugar are responsible for glycaemic overload and insulin resistance and this may lead to cellular growth promotion through specific hormones or IGFs. The role of fats, and of specific types of fats, in the risk of breast and colorectal cancers, as well as of several other cancers, remains a major open question (Hu et al., 2011a). In a large study from Italy, isocaloric substitution of 5% of the total calories from saturated fats by unsaturated ones was associated with reductions in the risk of breast (odds ratio = 0.67) and colorectal (odds ratio = 0.78) cancer (La Vecchia et al., 1998). The use of olive oil instead of butter and other added fats appears to be result in a decrease in the risk of various common cancers. In particular, there is suggestive evidence of a favourable effect on the risk of cancers of the upper aerodigestive tract. Olive oil is a major source of monounsaturated fats in Mediterranean countries, but also an important source of several micronutrients and food components that could be involved in cancer prevention (Pelucchi et al., 2011a). A risk-lowering diet for cancer would not only involve increasing the intake of fruit and vegetables and reducing the consumption of red meat (Hu et al., 2011b) but also the use of whole-grain carbohydrates in contrast to refined ones, and olive oil and other unsaturated fats instead of saturated ones.
The Mediterranean diet fulfils all these requirements as indicated in the well-known pyramid model (Fig. 1) (Bach-Faig et al., 2011). On the basis of data published by Trichopoulou et al., 2000, up to 25% of colorectal cancer, 15% of breast cancer and 10% of prostate, pancreas and endometrial cancer could be prevented if the populations of high-income countries could shift to the traditional healthy Mediterranean diet.
Moreover, the Mediterranean diet may help regulate body weight, which is a priority in cancer prevention. No

increase in overweight and obesity has been observed in Italy and France in the recent past (Gallus et al., 2006). From the point of view of potential preventive mecha- nisms, the analyses of the dietary pattern of the typical Mediterranean diet have shown a number of protective aspects such as a balanced ratio of n-6/n-3 essential fatty acids, high amounts of fibre, antioxidants (especially polyphenols from olive oil and wine) and vitamins E and C, some of which have been shown to be associated with a lower risk of cancer (Simopoulos, 2004).

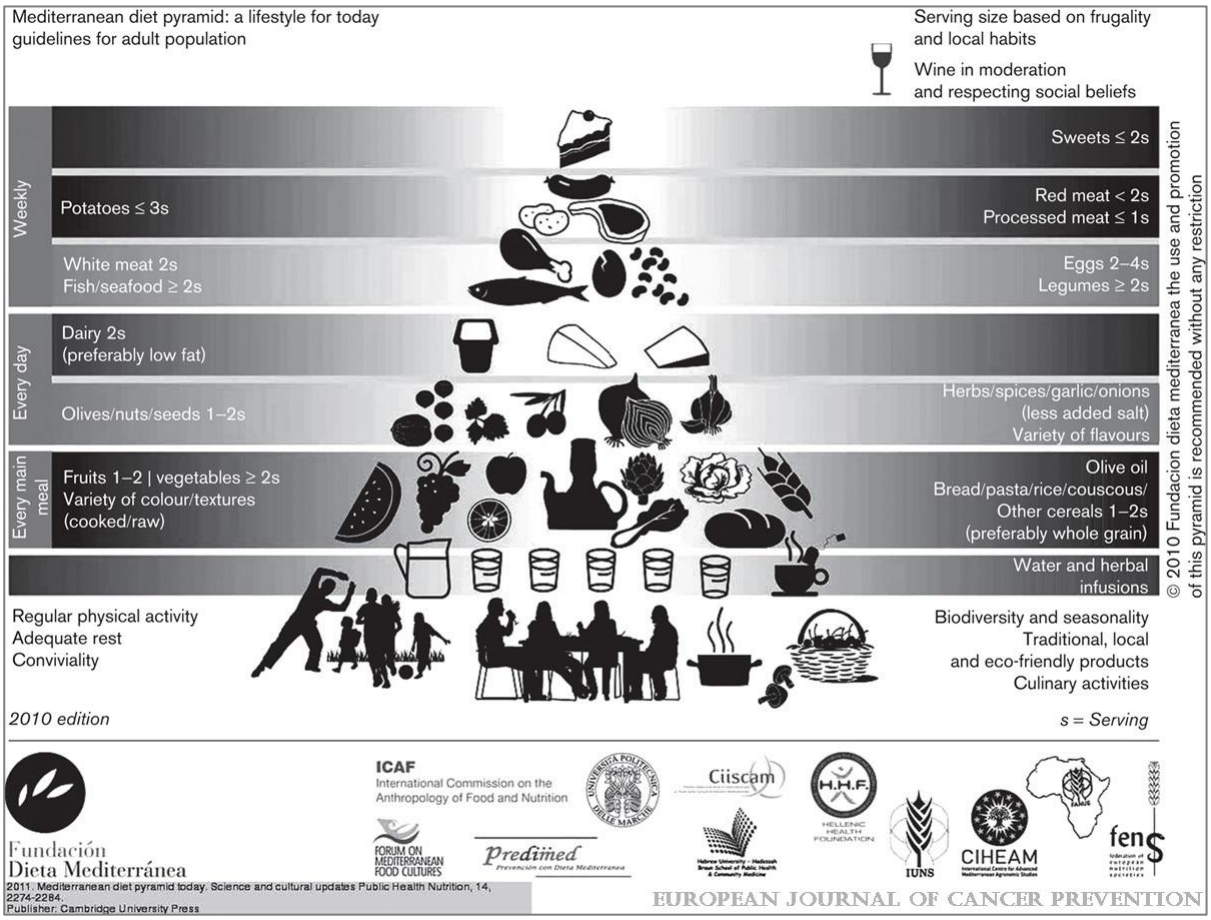

Fig. 1. The Mediterranean diet pyramid (Bach-Faig et al., 2011).

Alcohol and the risk of cancer

A total of 400 000 cases of cancer were attributable to alcohol drinking worldwide in 2002, representing 3.6% of all cancers (5.2% in men and 1.7% in women). The corresponding figure for mortality is 250 000 deaths (3.5% of all cancer deaths). This proportion is particularly high among men in Central and Eastern Europe. Among women, breast cancer comprises 60% of alcohol-attribu- table cancers (Boffetta and Hashibe, 2006; Boffetta et al., 2006). The consumption of alcoholic beverages increases, among others, the risk of cancers of the mouth and pharynx (apart from cancers of the salivary glands and nasopharynx) (Goldstein et al., 2010), oesophagus (squa- mous cell carcinoma) and larynx. The risk increases approximately in proportion to the consumed amount. Alcoholic beverages act synergistically with smoking, each agent approximately multiplying the effects of the other, and the main component of alcoholic beverages that determines the risk of cancer is ethanol (IARC Mono- graphs on the Evaluation of Carcinogenic Risks to Humans, 2004). In Europe and North America, cancers of the upper respiratory and digestive tracts are rare in the absence of smoking and only very few studies have included

sufficient number cases to provide useful information about the effect of alcohol by itself. There is no reason to assume that tobacco smoke is the only carcinogenic agent to which the human upper respiratory and digestive tracts are exposed, and ethanol may be facilitating the effect of some other unrecognized carcinogenic agents in nonsmokers. Acetaldehyde is a carcinogenic metabolite of alcohol (Doll, 1998; Baan et al., 2007; Secretan et al., 2009; Matsuo et al., 2012).

Heavy drinking is commonly associated with poor nutrition and this also increases the risk of cancer (particularly of pharyngeal and oesophageal cancer, but also of laryngeal cancer) in heavy drinkers (Doll, 1998). Cohort and case–control studies have consistently suggested a direct relation between consumption of alcohol and colorectal cancer. The relation, however, is moderate, the risk for both colon and rectal cancer being about 50% increased with high levels of alcohol con- sumption (Baan et al., 2007; Secretan et al., 2009).

Alcohol drinking is strongly related to cirrhosis and is associated with primary liver cancer. The relation is difficult to examine as most alcohol-related liver cancers arise from a cirrhotic degeneration, which in turn may lead to a reduction in alcohol drinking.

A recent meta-analysis has presented strong evidence for the absence of a role of moderate drinking in pancreatic carcinogenesis, as opposed to an increased risk for heavy alcohol drinking. Given the moderate increase in risk and the low prevalence of heavy drinkers in most populations, alcohol appears to be responsible only for a small fraction of all pancreatic cancers (Tramacere et al., 2010).

For breast cancer, Italian data, on the basis of a validated alcohol consumption questionnaire and a female popula- tion with a relatively high alcohol consumption, con- firmed that alcohol drinking is moderately related to the risk of breast cancer. This association could explain 12% (95% confidence interval, 5–19%) of breast cancers in Italy, thus representing one of the major avoidable risk factors for this neoplasm (Ferraroni et al., 1998). The association between alcohol consumption and the risk of cancer for those sites for which sufficient or limited evidence for carcinogenicity is available (IARC Mono- graphs on the Evaluation of Carcinogenic Risks to Humans, 2010) has been reviewed recently (Pelucchi et al., 2011b). On the basis of the data collected, it was concluded that the restriction of alcohol drinking to the limits indicated by the European Code Against Cancer (Boyle et al., 2003) (i.e. 20 g/day for men and 10 g/day for women) would be associated with a 90% reduction in cancers and cancer deaths that could be attributed to alcohol in men and over 50% of alcohol-attributable cancers in women. As a consequence, about 330/360 000 cancer cases and about 200/220 000 cancer deaths can be avoided worldwide every year (Boffetta et al., 2006). Avoidance or limitation of alcohol consumption to two drinks/day in men and one drink/day in women is therefore a global public health priority.

Mediterranean way of drinking and cancer

Alcohol consumption was traditionally high in Mediterra- nean countries, particularly in France and Italy, but substantial declines have been observed over the last three decades. The pattern and problem of alcohol drinking is also peculiar in these countries, with regular (rather than binge) drinking mostly at meals, and with wine being the most common type of alcoholic beverage in most regions. Excess consumption of alcohol has major implications for the risk of cirrhosis and a few cancer sites, including those of the upper digestive and respiratory tract. The incidence of and mortality from these cancers were remarkably high in the 1970 and 1980s in France, northern Italy and Spain. The total alcohol-related deaths (liver disease, cancer and car accidents) were estimated at B25 000/year in Italy (5% of all deaths) and over 50 000 (10% of all deaths) in France in the 1990s. Now these estimates are probably about 50% lower, because of the substantial (over 50%) decrease in alcohol consumption. This is not only because of declined mortality from cirrhosis and accidents but also because alcohol-related

cancer mortality has been declin- ing in France and Italy (Arfe` et al., 2011). Now the highest rates are reported in Central and Eastern Europe. In terms of risk assessment, high levels of alcohol consump- tion (i.e. more than four drinks/day) result in a substantial risk of cancer at several sites, whereas lower levels of consumption result in a moderately increased risk for various cancers.

At the same time, moderate alcohol consumption can exert protective effects against Hodgkin lymphoma and certain types of heart disease, and in particular, of ischaemic heart disease (Tramacere et al., 2012). Taking into account the favourable and unfavourable effects of alcohol on health, sensible individual advice should be provided on the recommended limits to alcohol drinking: these limits should not exceed 30 g of ethanol/day (i.e. about two drinks of beer, wine or spirits a day, meals included) for men and 15 g (one drink) for women.

Red wine, which is typically consumed in Mediterranean countries, contains a complex mixture of potentially preventive bioactive compounds (predominantly pheno- lic) and in particular flavonols such as myricetin, kaempferol and the predominant quercetin, the flavan- 3-ol monomers catechin and epicatechin, the oligomeric and polymeric flavan-3-ols or proanthocyanidins, various highly coloured anthocyanins, various phenolic acids (gallic acid, caftaric acid, caffeic acid, p-coumaric acid) and the stilbene resveratrol (Guilford and Pezzuto, 2011; Giacosa et al., 2012). Recent advances in viticulture and oenology research have allowed an increase in the concentration of phenolic compounds in grapes and wines (Cagnasso et al., 2008; Zamboni et al., 2010). Highly tannic red wines can contain up to 3 g of total polyphenols/l and the amount of catechin and epicatechin derivatives, including oligomeric procyanidins, can even reach B800 mg/l (200 mg in two glasses, i.e. 2.86 mg/kg for a man with a body weight of 70 kg) (Landrault et al., 2001) and the amount of resveratrol is B5 mg/l of wine (1.25 mg in two glasses of wine, i.e. 18 mg/kg for a man with body weight of 70 kg) (Stervbo et al., 2007). Moderate red wine drinkers will consume polyphenols at levels well above the population average. Resveratrol inhibits the proliferation of human cancer cell lines (Aggarwal et al., 2004; Baur and Sinclair, 2006; Vidavalur et al., 2006; Opie and Lecour, 2007; Harikumar and Aggarwal, 2008; Raval et al., 2008; Saiko et al., 2008) and, similar to curcumin and epigallocatechin gallate, it modulates the effects of deregulated cell cycle check- points (Meeran and Katiyar, 2008). A Danish cohort study of 156 patients with upper digestive tract cancers suggested that wine drinkers may be at a lower risk than those who have a similar intake of beer or spirits (Grønbaek et al., 1998; Gronbaek, 2002). Other studies, however, have shown inconsistent results (Boffetta and Hashibe, 2006).

More recently, in a study of 380 000 Americans, a Med- Diet score defined by high intake of fruits, vegetables, nuts, grains, and fish a low intake of dairy and meat and 5–25 g/day of alcohol showed a reduction in mortality for cardiovascular disease, in both men and women, when the highest versus the lowest score tertiles were compared (Mitrou et al., 2007). This study also confirmed that the Mediterranean food pattern is associated with decreased cancer mortality (Mitrou et al., 2007).

Grinzane consensus on 'Mediterranean diet and cancer prevention: food and wine for a healthy lifestyle'

A forum held in Grinzane Cavour (Italy) in November 2011 explored the crucial questions on how to modify the risk of cancer by the diet and resulted in the following consensus statement, signed by the authors of the present editorial: (a) the Mediterranean diet is char- acterized by the use of olive oil, frequent consumption of fruit and vegetables, fish, pulses and unrefined cereals, moderate intake of dairy products and a low intake of red and processed meat, with a moderate consumption of wine at meals. Nuts, spices and herbs are commonly used.

(b) The Mediterranean diet is associated with a reduced risk of cardiovascular disease and cancer. (c) If the Mediterranean diet were introduced in countries with a typical western diet, the overall risk of cancer could be reduced by 10% and in particular the risk of colorectal and other digestive tract cancers can be reduced by up to 25%. (d) The biological mechanisms for cancer preven- tion associated with a Mediterranean diet have been related to the favourable effect of a balanced ratio of omega 6 and omega 3 essential fatty acids and the high amounts of fibre, antioxidants and polyphenols found in fruit, vegetables, olive oil and wine. (e) The Mediterra- nean diet also involves a 'Mediterranean way of drinking', that is, a regular, moderate consumption of wine mainly with food (up to two glasses a day for men and one glass for women). This pattern of drinking increases longevity, reduces the risk of cardiovascular disease and does not markedly influence the overall risk of cancer.

Acknowledgements
The work of C.L.V., E.N. and C.P. was supported by the Associazione Italiana per la Ricerca sul Cancro (AIRC).

Conflicts of interest
There are no conflicts of interest.

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