Nutrition and Prevention of Diseases

Module 20.3

Nutrition in the Prevention of Cancer

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Learning objectives

• To understand the potential of nutrition in cancer prevention;
• To understand specific behaviours that can modify cancer risk;
• To gather insights into the role of gene-diet interaction in determining response to dietary components.

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Key Messages

• Cancer is a preventable disease;
• Environmental factors play a prominent role in increasing cancer risk;
• Diet, physical activity and maintenance of a healthy weight can prevent 40% of all cancers;
• Fruit, vegetables, and fibre have a protective effect, whereas high-temperature cooked red meat and processed meat increase the risk of developing cancer;
• There is no evidence that vitamin supplements help to prevent cancer.
1. Introduction

Despite the amount of resources put into discovering a genetic origin for cancer, epidemiological and experimental research keeps strengthening the notion that cancer is a disease largely caused by environmental factors. Classical genetics alone cannot explain the diversity of phenotypes within a population. Nor does classical genetics explain how, despite identical DNA sequences, monozygotic twins and cloned animals have different phenotypes and show different susceptibilities to diseases. Even changes in genetic susceptibility to cancer due to genetic polymorphisms cannot have occurred over one generation, and studies of migrant populations consistently highlight the role of exogenous factors through gene–environment interactions. The environment plays a more important role in cancer genesis than is usually acknowledged. Rather than winning the “war on cancer” we are facing a global cancer epidemic: on December 9, 2008, the International Agency for Research on Cancer (IARC) in an event held in Atlanta, Georgia, released updates on cancer death projections. According to the report, between 1975 and 2000 cancer cases doubled, they will double again between 2000 and 2020, and nearly triple by 2030. In 2010, cancer was due to become the leading cause of death worldwide (1). Since almost two-thirds of all cancers can be prevented by lifestyle modifications, physical activity, proper diet and maintenance of a healthy weight (2, 3), it is an imperative to consistently redirect public health policies, government programmes and research funding from cancer treatment and diagnosis to primary cancer prevention if we want to halt current growing trends.

2. Cancer Numbers

In 2002, more than 10 million new cases of cancer were recorded worldwide, with nearly 7 million cancer deaths. These numbers are destined to grow. Projections estimate an almost tripling of new cases by 2030, with approximately 13 to 17 million deaths (1). Such a dramatic increase can only be partly attributable to a growing global population, an increase in life expectancy and progress in diagnosis and screening. The rising incidence of cancers in fact, is documented across all age categories, including children and adolescents, the fetus being particularly vulnerable to exogenous factors. Of particular concern is the steady raise in childhood cancers observed over the past three decades, and the acceleration of this trend, with a documented 1 percent and 1.5 percent average annual increase in children and adolescents, respectively (4) (Fig. 1).

![Fig. 1](image_url)  
Fig. 1 Age-specific incidence rates of cancer in children and adolescents in Europe: p values test difference between first and last decade (from Steliarova-Foucher E. et al, Lancet 2004, reproduced with permission)
Concomitantly, the economic burden of cancer is substantially increasing: in the year 2008, the National Institutes of Health estimated overall annual total costs of cancer in 2007 in the U.S. at $219.2 billion (5). Of note in 2007, six million new cases of cancer – more than half of the eleven million cases reported worldwide, occurred in low- and middle-income countries (6), which simply lack the resources to sustain the economic costs associated with cancer screening and treatment.

### 3. Cancer as a Preventable Disease

During the past few decades, a broad range of in-depth studies have provided conclusive evidence on the pivotal role of food and nutrition (or specific food constituents), in cancer prevention. The combined scientific data derived from epidemiological, interventional and experimental studies concerning food, nutrition, overweight, physical activity and other environmental factors, clearly suggest that, at least to a certain degree, cancer is a preventable disease. Worryingly enough, it has been recently pointed out that in spite of a general scientific consensus on the importance of a healthy diet for cancer prevention, the eating habits of pre-adolescents and adolescents are not aligned with dietary recommendations. These discrepancies between expert recommendations on diet and cancer and actual dietary practices in the young point to the need for more research to better promote the translation of science into practice (7).

In 1997 the WCRF/AICR published its first report on *Food, Nutrition and the Prevention of Cancer: a Global Perspective*, which has become the most authoritative statement on the topic (2); in 2007 review of the updated literature resulted in the publication of a second WCRF/AICR document entitled *Food, Nutrition, Physical Activity, and the Prevention of Cancer: a Global Perspective* (3). The first report, having analysed all available literature on cancer and the environment concluded that “cancer is principally caused by environmental factors, of which the most important are tobacco, diet and factors related to diet, including body mass and physical activity, and exposures in the workplace and elsewhere.” The same report concluded that 30 to 40 percent of all cancers are directly linked to dietary choices. Since the mid 1990s there has been a dramatic increase in the amount of literature on this subject, concerning particularly the effects of overweight, obesity and physical activity. Review of the new data confirmed that approximately 40% of all cancers are linked to poor diet, physical inactivity, and excessive body weight. If we apply these percentages to the more than 12 million new cancers that occurred in 2007 worldwide (8), we can estimate that over 4 million people could have been spared the tragedy of cancer by the very feasible approach of eating, weight control and exercise outlined in the report recommendations. These numbers present a pressing challenge to scientists and health policy-makers to invent, develop and launch measures that will effectively prevent cancer through promotion of healthy lifestyles and reduced exposure to risk factors. This can be accomplished through reorientation of public health priorities from treatment and diagnosis to primary prevention, which will be necessary if the goal of comprehensive cancer control through reduction of cancer burden and suffering is to be accomplished.

### 3.1. Cancer and the Environment

For decades research has looked into the genetics of cancer to find solutions to the cancer riddle. The discovery of oncogenes, tumour suppressor, DNA repair and cancer susceptibility genes has led in the past to the conclusion that cancerogenesis is a purely endogenous genetic process. More recently, however, advances in the field of epigenomics, transcriptomics, proteomics and metabolomics have given a wider picture of the cancer process, which is presently considered the result of a complex interaction between cells and environmental factors.
Cancer development is a multistep process. It is the result of a series of DNA alterations in a single cell, or clones of that cell, which lead to loss of normal function, aberrant or uncontrolled cell growth and often metastases. With the exception of the rare familial cancers which are primarily caused by inheritance of a specific germline mutation, sporadic cancers may acquire mutations as a result of genotoxic exposure to external or internal agents and consequent DNA damage. The likelihood that a mutation occurs and persists in subsequent clones is heavily dependant on the efficiency with which potentially toxic exposures to carcinogens or co-carcinogens are metabolized and excreted, as well as on the efficiency of the enzyme machinery in charge of repairing DNA replication mistakes. This ability varies considerably among individuals because of the population variability in the polymorphic genes that regulate these processes. While inherited gene mutations are responsible for only a small fraction of the cancer burden, accounting for 5-10 percent of all cases, inherited variants of genes encoding enzymes involved in the activation or detoxification of exogenous carcinogenic factors and in the repair of subtle mistakes in DNA structure are much more frequent. These genes indeed, are polymorphic in nature, and may account for individual differences in cancer susceptibility. That is to say that the risk of cancer associated with a particular environmental exposure differs with respect to functionally different polymorphisms of certain genes, i.e., gene-environment interaction. The realization that genetic and environmental factors work in concert, as co-determinants of cancer susceptibility represents a new paradigm in cancer risk assessment and opens a new window of opportunity for cancer treatment and control.

3.2 Evidence from Ecological Studies

Ecological studies examine relationships between environmental factors and disease among populations rather than individuals. They contribute to the identification of determinants of both individual and population health that warrant further investigation. The cancer pattern (the distribution of different cancers) varies between countries and populations. Some cancers are more prevalent in lower income countries, others in higher income countries. Also, cancer patterns change in time within countries and populations, for instance, if countries become more urbanized and industrialized, or if populations migrate to other countries. Such changes highlight the important role of environmental factors as cancer risk modifiers. Studies on migrant population have provided some of the most compelling evidence, suggesting not only that the main causes of cancer are environmental, but that food, nutrition and maintenance of a healthy weight each plays a major role.

Assessment of breast cancer risk in women who have migrated from countries with a low incidence of breast cancer to countries with high breast cancer rates is a typical example of migrant studies. In foreign-born Hispanics who moved to the San Francisco Bay Area, breast cancer risk was 50% lower than in U.S.-born Hispanics. The risk increased with increasing duration of residence in the U.S. and with decreasing age at migration (9).

Similarly, stomach cancer mortality in migrants from the Former Soviet Union (FSU), a high-risk area, to Germany and Israel remained elevated after migration but started to decline during a study period ranging from 1990 to 2005 in Germany and from 1990 to 2003 in Israel. Converging mortality rates between migrants and the general population in Germany and Israel are such that mortality from stomach cancer among migrants from the FSU is expected to reach rates similar to those of the host countries in a few years (10).

More data from recent migrant studies demonstrate that in second-generation immigrants, cancer incidence rates generally become similar to those of the host country. This was shown in first- and second-generation immigrants to Denmark, a country with a high-incidence of testicular cancer. In first-generation immigrants testicular cancer risk was much lower than that in native-born Danes and reflected risk in the countries of origin, whereas the risk in second-generation immigrants was similar to that in natives of Denmark. The fact that risk in first-generation immigrants was not modified by age at immigration or duration of stay, argues
for a substantial influence of environmental factors limited to exposure in early life, most probably in utero exposure (11), in the development of testicular cancer.

Another important study also showed that in second-generation immigrants cancer incidence rates generally become similar to those of the adopted country. In first generation immigrants to Sweden incidence of all cancers was 5% and 8% lower for immigrant men and women, respectively, compared with native Swedes (12). However, within one generation, total cancer incidence approached figures for people native to Sweden (12). Analysis of the data led the authors to the conclusion that “Birth in Sweden sets the Swedish pattern for cancer incidence, irrespective of the nationality of descent, while entering Sweden in the 20s is already too late to influence the environmentally imprinted program for the cancer destiny” (13).

Ecological and migrant studies consistently indicate that the main determinants of cancer patterns are modifiable, and that environmental exposure during prenatal and early life has a fundamental role in cancer induction. Such conclusions are supported by the results of thousands of epidemiological and experimental studies, thoroughly reviewed in the first and second WCRF/AICR expert report, which have highlighted the pivotal role of patterns of food, nutrition, body composition and physical activity in cancer control. As more is learned about how early life factors relate to childhood, adolescent and adult cancer risk, appropriate dietary interventions can be developed and targeted to the short-terms of pregnancy and early postnatal life before trying to alter diets and behaviours over longer periods of time.

### 3.3 When More is Better

The interaction between environmental factors, diet, nutritional status, lifestyle and the incidence of cancer and other chronic diseases is presently being tested in the largest prospective cohort study ever undertaken, the European Prospective Investigation of Cancer (EPIC), a long-running study of diet and health. Study recruitment was carried out between 1993 and 1999 and follow up planned for at least ten years. Dietary information and blood was collected from over half a million (520,000) individuals living in ten European countries: Denmark, France, Germany, Greece, Italy, The Netherlands, Norway, Spain, Sweden and the United Kingdom. While the trial and its analysis is still ongoing, some of the key results already published show how several environmental factors are seemingly having a pivotal role on cancer incidence. Above all stands the recent finding that the combined impact of four healthy behaviours – not smoking, not being physically inactive, moderate alcohol intake and consumption of at least five fruit and vegetable servings a day – predicts a 4-fold difference in total mortality in men and women (14). The trends reported in the study, while being strongest for deaths from cardiovascular disease, were also apparent for deaths from cancer and from other causes. The magnitude of the combined impact resulting from these four behaviours translated into an estimate of being 14 years younger than chronological age, which was significantly a greater effect than that expected from each individual risk factor, indicating that health behaviours act synergistically on pathways implicated in maintenance of proper biological functions.

On the same lines are the results of a longitudinal study conducted on elderly European individuals aged 70-90 years, which investigated single and combined effect of four factors: Mediterranean diet, being physically active, moderate alcohol use, and non-smoking, on all-cause and cause-specific mortality. During a 10-year follow-up, individuals with 2, 3 or 4 healthy behaviours had less than half the mortality rate from all causes, coronary heart disease, cardiovascular diseases, cancer and from other causes, than those with 0 or 1 such behaviour. For cancer specific mortality, 60% of deaths during the 10-year follow-up period were associated with not adhering to this low-risk pattern (15). The more healthy behaviours adopted by individuals, the lower the risk of cancer-specific mortality (Table 1).
Table 1

<table>
<thead>
<tr>
<th>Number of protective factors</th>
<th>Cancer</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0-1</td>
<td>(n=246)</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>(n=702)</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>(n=954)</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>(n=437)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>1.00</td>
<td>0.62(0.51-0.75)</td>
</tr>
<tr>
<td>PAR (%)</td>
<td>14</td>
<td>38</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; HR, hazards ratio; PAR, population attributable risk.

These data provide further support to the idea that achievable differences in lifestyle may result in substantial differences in mortality risk in the population. Establishing a causal relationship would require an interventional study, and the number of years an individual needs to maintain such a lifestyle to realize a benefit is unknown. However, the notion that the combination of adopting a healthy diet rich in fruit and vegetables, with moderate alcohol consumption, avoiding physical inactivity, and not smoking, is associated with substantial lower mortality rate, even in old age, may encourage behavioural change at the population level.

4. Results from the Second WCRF/AICR Expert Report

Evidence that different foods and their constituents modify cancer risk and tumour behaviour is widespread. However, unravelling links between diet and cancer is complex, as shown by the numerous inconsistencies reflected in the literature. The origins of these discrepancies are multifactorial, and reflect the ample variations in food constituents according to soil status, seasonality, storage conditions, transportation, processing and preparation, the variability in their absorption, metabolism or site of action due to genetic polymorphisms, the modification of gene expression and biological response by DNA methylation patterns and other epigenomic events, just to name a few examples. In addition, dietary components have the ability to modify all major signalling pathways – metabolism of carcinogens, DNA repair, cell proliferation, apoptosis, inflammation, immunity, differentiation, angiogenesis, hormonal regulation and cellular energetics, etc. – in both normal and cancer cells; hence evaluation of the overall impact of the thousands of dietary constituents taken with/as food, is a massive task.

Given these premises, systematic review of all the critical literature published on the issue and summarized in the 2007 WCRF/AIRC second expert report has again confirmed, 10 years after the first report, the essential role of food, nutrition and body composition in modulating cancer initiation, promotion and progression (3).

The major findings of the report are:

- Dietary fibre from unrefined cereals, legumes, vegetables and fruits probably protects against colorectal cancer. There are several mechanisms which may explain the protective role of fibre including increasing faecal weight, decreasing transit time, binding to carcinogens, alteration of the gut environment through lowering of faecal pH, stimulation of bacterial fermentation and production of short chain fatty acids, particularly butyrate, capable of inducing apoptosis, cell cycle arrest and cell differentiation. Although such mechanisms are plausible, the report concluded that residual variables cannot be excluded. Of note, results of a recent prospective study of 63,550 men and women recruited in the EPIC-Oxford study in the UK in the 1990s, showed that unlike total cancer incidence, which is lower in vegetarians than in non-
vegetarians, colorectal cancer incidence is significantly higher in vegetarians compared to meat eaters (16). Since vegetarians are likely to consume a diet high in fibre, this result adds new uncertainties into the assessment of the true value of dietary fibre in colon cancer prevention.

- There is ample and consistent evidence that foods contaminated with aflatoxins are a cause of liver cancer. Aflatoxins are a type of mycotoxins classified as human carcinogens (group 1) by the IARC. Contamination involves mainly cereals and legumes (especially peanuts), followed by nuts and seeds, and is more frequent in countries with damp climates and poor storage conditions. Aflatoxins are converted to their carcinogenic forms, through metabolism by members of the cytochrome P-450 enzyme superfamily, to intermediates, which act as carcinogens through covalent interaction with cellular DNA and proteins. There is evidence that genetic polymorphism in the glutathione S-transferase (GST) family of metabolising enzymes is a factor in individual susceptibility to aflatoxin-induced hepatocarcinogenesis, since this may regulate an individual's ability to metabolize the ultimate carcinogen of aflatoxins (17).

- Non-starchy vegetables and fruits probably protect against upper aerodigestive tract (mouth, pharynx, larynx, oesophagus and stomach) cancer. There is a significant inverse association between fruit consumption and lung cancer risk in both smokers and non-smokers. High vegetable intake significantly decreases lung cancer risk in current smokers (18). Among individual plant foods, plant food groups and food constituents, apples, pears, citrus fruit, cruciferous vegetables and carotenoids from foods appear the most protective toward lung cancer risk (3,17). While the majority of studies show decreased risk of these cancers with increased intake of fruit and vegetables, the overall evidence remains contradictory. A possibility is that there may be a threshold of fruit and vegetable intake below which cancer risk is increased. Still, many countries have adopted national recommendations for consumption of five or more servings per day of fruit and vegetables. The possible protective effects of fruit and vegetables might involve their high levels of micronutrients (including antioxidants), which can decrease DNA damage by scavenging for oxygen radicals. Foods that are high in antioxidants tend to be inversely associated with the risk of upper GI malignancies and telomere length. Telomere length is associated with cumulative oxidative stress from environmental factors, and telomerases are shorter in persons with gastric cancer. Fruit and vegetables might also have positive effects because they contain flavones, which inhibit the cell process associated with carcinogenesis (adhesion, invasion, and migration), possibly through their effects on focal adhesion kinase and metalloproteinases (19).

- Red meat and processed meat (meat preserved by smoking, curing, salting, or by the addition of preservatives) is a cause of colorectal cancer. Most epidemiological data linking red meat to colon cancer risk relate to the way meat is cooked and preserved. Cooking meat at high temperatures (i.e., frying, grilling, and barbecuing) induces heterocyclic amine formation, and polycyclic aromatic hydrocarbons are formed in meat and fish that has been broiled or charbroiled over direct flame. Nevertheless, these compounds are ubiquitous in the diet – cereals, oils and fats being the major sources. Also, processed meat may contain nitrates and nitrites. Nitrate (NO₃) is an inorganic compound that occurs under a variety of conditions in the environment, both naturally and synthetically. Vegetables, meat products, fish products, beer and contaminated groundwater are major sources of nitrates. Nitrates are essentially non-toxic but can be reduced to nitrites (NO₂) either in improperly stored food, or in the body. The main site of reduction is the mouth and the stomach, and to a lesser extent the lower intestine. The nitrites from these and other sources, including those purposely added to food for preservation due to their toxicity upon bacteria, present a toxic hazard both by their direct toxicity and by formation of carcinogenic N-nitroso compounds (nitrosamines) from reaction with amino compounds. Nitrosamines may be formed in meat during the curing process or in the body from dietary nitrates or nitrites; they are recognized
carcinogens. Finally, haem iron present in red meat has been shown to catalyse formation of N-nitroso compounds in the intestine.

- Milk and more significantly dietary calcium (from dairy foods, vegetables, nuts, pulses and fish or meat cooked on the bone) protects from colorectal cancer. Total cheese intake may however increase colon cancer risk, and high dietary intake of calcium is a probable cause of prostate cancer. The evidence is consistent with a dose-response relationship.

- There is limited evidence that diets high in fats may be a cause of postmenopausal breast cancer. This conclusion is supported by recent results of a prospective trial in European women enrolled in the EPIC study, indicating a weak positive association between saturated fat intake and breast cancer risk in postmenopausal women, particularly in those who had never used hormone replacement therapy (20). Significant correlations have recently been observed between basal DNA damage and dietary fat sources, damage being positively correlated with the ratio of ω-6 PUFA to ω-3 PUFA, as well as to the intake of red and processed meats, and dairy products (21). On the other hand growing evidence supports the protective role of a high ω-3 to ω-6 fatty acid ratio, which has been associated with a reduced risk of cancer, especially breast cancer, and with improved prognosis. ω-3 fatty acids exert anti-angiogenic effects and have anti-inflammatory and immunosuppressive properties reducing inflammation through different mechanisms. In particular, EPA (eicosapentaenoic) and DHA (docosahexaenoic) ω-3 fatty acids partially replace arachidonic acid as eicosanoid substrate in all cell membranes, but especially in erythrocytes, neutrophils, monocytes and liver cells, thus suppressing the production of ω-6 pro-inflammatory eicosanoids. In addition, EPA and DHA suppress the NF-κB pathway and modulate plasma membrane micro-organization (lipid rafts), in particular relative to the function of Toll-like receptors (TLRs), and T-lymphocyte signalling molecule recruitment to the immunological synapse (22).

- Excessive salt and sodium intake in general can increase the risk of stomach cancer. This finding is supported by biological plausibility. Excess salt intake may damage the lining of the stomach, increase formation of nitrosamines and enhance activity of carcinogens in the stomach. In addition, a high salt diet may facilitate H. pylori infection, an established cause of stomach cancer. WCRF recommends limiting salt intake to a maximum of 5 grams per day, taking into account total sodium intake from all dietary sources.

- There is a strong, significant association between exposure to water contaminated with inorganic arsenic - arising from agricultural and industrial practices or naturally occurring - and increased lung cancer risk. The effect size is relatively large.

- Consumption of alcohol, including wine, significantly increases the risk of cancer in the upper aerodigestive tract (oral cavity, pharynx, larynx, oesophagus), the colorectum and the breast. Risk increases in a linear fashion with increased intake, with no “safe level” of consumption (23). There are several mechanisms by which alcohol may increase cancer risk. Ethanol is mostly metabolized by oxidation to acetaldehyde and acetate, catalysed principally by alcohol dehydrogenase (ADH) and aldehyde dehydrogenase (ALDH). Acetaldehyde is a weak mutagen and a carcinogen, causing point mutations, sister chromatid exchanges and gross chromosomal aberrations. There is large inter- and intra-individual variability in alcohol metabolism, due to genetic and environmental factors. Individuals of northeast Asian heritage, for example, may have a dominant mutation in their acetaldehyde dehydrogenase genes (specifically, the mitochondrial ALDH2 gene) making this enzyme less effective at metabolizing acetaldehyde (24). Polymorphisms and mutations in ALDH and ADH may increase individual risk of contracting cancers of the oesophagus, elsewhere in the upper aerodigestive tract and colorectum associated with alcohol consumption, due to
acetaldehyde overexposure (25-28). Ethanol is also oxidized through catalase and cytochrome P450 2E1 pathways. Not only ethanol is a substrate of CYP2E1, but it is also a potent inducer of this enzyme, thereby increasing oxidative stress and the conversion of procarcinogens to carcinogens. Alcohol may therefore act as a co-carcinogen by enhancing the effects of carcinogens such as those found in tobacco and the diet. Furthermore, alcohol may act as a solvent, enhancing penetration of other carcinogens into cells. Another possible explanation of alcohol cocarcinogenic effect is that alcohol overconsumption is often linked to nutritional deficiencies, thus making cells more susceptible to carcinogenesis. The expert panel highlighted how evidence that alcohol consumption increases cancer risk at many sites has become stronger since the publication of the first expert report.

- Regarding supplements, the report confirms that high dose beta-carotene supplements increase lung cancer risk, that calcium probably protects against colorectal cancer, and that selenium at specific doses and in selected individuals probably protects against prostate cancer, and possibly against lung and colorectal cancer.

- Overweight and obesity is a cause of cancer of the colorectum, breast (in post-menopausal women), endometrium, oesophagus, pancreas and kidney. Central obesity is a cause of colorectal cancer and a probable cause of endometrial and postmenopausal breast cancer. There are several mechanisms by which excess body fatness increases cancer risk, including increased inflammatory response, alterations in the metabolism of endogenous hormones with increased circulating levels of oestrogens, insulin, insulin-like growth factor (IGF)-1 and IGF-binding proteins and accumulation of environmental chemical carcinogens in the adipose tissue. Data from a large trial conducted by the American Cancer Society on a population of more than 900,000 U.S. men and women estimated that overweight and obesity in the U.S. may account for 14% of all deaths from cancer in men and 20% of those in women (29). Although the number of overweight and obese adults is higher in developed countries, it is also rapidly growing in the developing world. Of even more concern is the increasing number of overweight and obese children worldwide, with 22 million children under age five estimated to be overweight. These data, combined with the rising worldwide trend of excess weight, suggest that overeating may represent the most important avoidable cause of cancer in non-smokers. WCRF recommendations aim at maintaining body mass index between 21 and 23.

- Dietary pattern and the Mediterranean Diet. In the literature, there are various definitions of the Mediterranean Diet (MD) but they generally share the main components: a high consumption of vegetables, fruit, whole grains, legumes, olive oil and fish (especially marine species), a low intake of saturated fats such as butter and other animal fats, red meat, poultry, dairy products, and a regular but moderate consumption of ethanol mainly consisting of red wine during meals. Some of these features overlap with other healthy dietary patterns, whereas other aspects are unique to the MD. The MD is characterized by a high content of “good fats”, monounsaturated (MUFA) and polyunsaturated (PUFA) fatty acids, present in marine fish, vegetable oils (especially olive oil), in nuts and seeds, and by a low intake of saturated fatty acids and hydrogenated oils (trans fats). In particular, the MD provides an optimal dietary fat profile characterized by a low intake of saturated and ω-6 fatty acids and a moderate intake of ω-3 fatty acids. The ratio between ω-6 and ω-3 PUFAs plays an important role in the modulation of inflammation and blood coagulation and is one of the most powerful anti-inflammatory features of this diet. In terms of micronutrients, the MD is rich in B vitamins (B1, B2, niacin, B6, folate and B12), antioxidant vitamins (vitamins E and C) and minerals, especially iron, selenium, phosphorus and potassium. Plant foods constitute the core of MD and are characterized by a high content of “non-nutritive” components (phytochemicals), including polyphenols, phytoestrogens and carotenoids. The MD modulates multiple interconnected processes involved in carcinogenesis and
inflammatory response such as free radical production, NF-κB activation and expression of inflammatory mediators, and the eicosanoids pathway. In particular the MD is capable of affecting the balance between pro- and anti-inflammatory responses as well as promoting gut microbiota homeostasis and modulating oncogenesis through specific microRNAs. Indeed, growing evidence indicates the beneficial and preventive role of the Mediterranean Diet in the onset of cancer and other diseases associated with increased level of inflammation, oxidative damage and angiogenesis. A recent meta-analysis of all the observational studies regarding adherence to a MD in relation to cancer risk (30) showed that the MD is associated with a significant reduction in overall risk of cancer incidence and of mortality by 10%. In particular, increased adherence to the MD reduces the likelihood of having colorectal cancer (CRC), even among obese and diabetic patients, suggesting potential benefits of this dietary model on CRC risk factors. The high content of fibre typical of the MD is probably at the base of this reduced incidence of colorectal cancer. Contrasting data are reported for other forms of neoplasm. As far as concerns breast cancer, it is worth noting that the protective effect of the MD against breast cancer seemed to depend on the individual’s other characteristics and potential risk factors, such as obesity, physical activity, smoking, age at the menarche, and menopausal status (31).

5. Food Contaminants and Food Additives

Thousands of chemical substances, some of them with carcinogenic properties, contaminate the food supply. They include chemicals added to modify flavour, colour, stability or texture, residues of pesticides, and drugs given to animals. The majority of these substances has never been tested for carcinogenicity. In addition, chemical contaminants may be formed during food preparation or find their way into foods during industrial processing and packaging. Food can also be contaminated by naturally occurring carcinogens such as mycotoxins from mould growth, and aflatoxin is a definite cause of liver cancer, as previously reported. The role of carcinogens in foods with respect to cancer risk is largely unknown and difficult to assess, since these compounds are multiple, diverse and pervasive in the environment. Biological and toxicological data must be analysed in close relationship with genetic susceptibility, in order to interpret epidemiological studies in a more comprehensive and informative way.

Among all substances, effects of acrylamide recently gained momentum as a potential public health concern. Acrylamide is a proven rodent carcinogen and probable human carcinogen. In Europe its concentration in water is strictly regulated to maximum levels of 0.1 microgram per litre. In 2002, after a tunnel construction accident in Sweden, high concentrations of acrylamide were detected in tunnel construction workers as well as in non-exposed individuals serving as controls. These high levels in unaffected individuals were suspected to derive from dietary sources. Indeed chemical analysis demonstrated substantial levels of acrylamide in various heat-treated carbohydrate-rich foods. Biochemical analysis showed that during food processing at temperatures above 120°C, free asparagine and sugars react together with the formation of acrylamide. Acrylamide levels in food vary widely depending on the manufacturer, the cooking time, and the method and temperature of the cooking process. Potato chips, French fries, certain brands of cookies and breakfast cereals contain very high levels of acrylamide compared with other foods. The average content in potato crisps and French fries of approximately 750 microgram/kg and 330 microgram/kg, respectively, may, in some samples, reach concentrations up to ten times higher (32). Other food groups which may contain low as well as high levels of acrylamide are coffee, crisp-bread, breakfast cereals, biscuits, cookies and snacks such as popcorn. The high concentrations reported in several commonly consumed foods, several order of magnitude higher than those permitted in drinking water, are reason for serious concern, especially considering that children, a particularly vulnerable population, tend to have high estimated daily intakes of these products, 2–3 times greater than those of adults, based on average body weight ratios (30). The epidemiological studies conducted so far generally do not support a role for dietary acrylamide on endometrial, ovarian, breast, colorectal and prostate cancer risk. When haemoglobin
adducts of acrylamide were used as biomarkers of exposure, however, a positive association was seen between acrylamide-haemoglobin levels and oestrogen receptor positive breast cancer in post-menopausal women (33). Since studies using recovery biomarkers have indicated that measurement errors from dietary assessment instruments are usually larger than previously thought, it is clear that more data using concentration biomarkers as proxies for acrylamide exposure are needed, in order to properly evaluate its true carcinogenic risk in humans.

6. Protective Dietary Components

Foods contain a wide range of compounds with documented chemopreventive activity, some of which are known as phytochemicals. Phytochemicals confer particular properties to foods, such as taste and colour and possess in various degrees anti-oxidant, anti-carcinogenic, anti-inflammatory, immunomodulant and antimicrobial effects. According to their chemical structure and functional characteristics they are grouped in different families which include:

Carotenoids. This family of compounds comprises the pro-vitamin A alpha-carotene, beta-carotene and beta-cryptoxanthin, as well as lycopene, lutein and zeaxanthin. Carotenoid-rich foods include carrots, apricots, peaches, cantaloupe melon, sweet potatoes, winter squash, kale, spinach, romaine lettuce and broccoli. Consuming five or more servings of fruit and vegetable per day provides approximately three to six milligrams of beta-carotene. Carotenoids act as antioxidants (lycopene being the most potent) and immune-enhancers; the retinoid (vitamin A) precursors may be converted to retinol and stimulate cellular differentiation and activation of carcinogen-metabolising enzymes. After reviewing available literature on the role of carotenoids in cancer prevention, WCRF in its second expert report concluded that there is considerable evidence that foods containing carotenoids protect against upper aerodigestive tract cancers, lung and prostate cancer (lycopene). The protective effects of dietary carotenoids upon lung cancer risk stimulated randomized trials of high dose (20-30 milligrams per day) synthetic beta-carotene for lung cancer prevention in smokers. Results of these trials, reviewed in a recent meta-analysis, revealed however that high dose synthetic beta-carotene supplementation in current smokers increases lung cancer risk and lung cancer death (34).

Isothiocyanates. This class of sulphur-containing phytochemicals occur naturally as glucosinolate conjugates in cruciferous vegetables, which are released through hydrolysates by the enzyme myrosinase after plant cell rupture. Isothiocyanates are found in cruciferous vegetables such as broccoli, cauliflower, kale, turnips, collards, Brussel sprouts, cabbage, radishes, and watercress, and are responsible for the typical flavours of these vegetables. Isothiocyanates exert anti-cancer properties by inhibiting cell proliferation and inducing apoptosis; they are also potent inducers of the liver's Phase II enzymes, involved in carcinogen detoxification. Isothiocyanates are excreted by the kidneys after conjugation to glutathione by glutathione S-transferases (GSTs), most notably GSTM1 and GSTT1. Polymorphic variants of the GSTM1 and GSTT1 genes include a deleted or ‘null’ allele. When individuals are homozygous for the null allele they do not produce an active enzyme and therefore accumulate higher isothiocyanates levels in the blood. Epidemiologic evidence supports a role for cruciferous vegetables in the prevention of cancer at different sites. This effect is especially pronounced in individuals with homozygous deletion for GSTM1 and GSTT1. A systematic review of all epidemiological literature through to December 2007 analysing the association between lung cancer and cruciferous vegetable intake, found a 17 to 22% lower risk of lung cancer in individuals with a high intake of cruciferous vegetables, compared to those with low intake (35). In individuals with GSTM1 and GSTT1 double null genotypes, risk reduction approached 60%. In a large, prospective study of fruit and vegetable intake and prostate cancer risk, cruciferous vegetables, particularly broccoli and cauliflower, significantly reduced risk of aggressive prostate cancer (36). A recent article provided experimental evidence in support of epidemiological data that intake of cruciferous vegetables reduces prostate cancer
risk, by showing that a broccoli-rich diet causes perturbation of TGFβ1, EGF and insulin signalling pathways in the human prostate gland, each of which is associated with prostate carcinogenesis (37). Perturbation of signalling pathways is influenced by GSTM1 genotype. Additional epidemiological evidence further points toward a protective role of cruciferous vegetables against gastric, colorectal, ovarian and bladder cancer. Because of these gene-diet interactions, future studies need to investigate their associations with homozygous deletion of GSTM1 and GSTT1 to gather clearer knowledge on the potential role of isothiocyanates in cancer prevention.

**Flavonoids.** Flavonoids are polyphenolic compounds ubiquitously found in plants and which are responsible for their pigmentation. Flavonoids are categorized according to chemical structure into many different chemical groups of substances including flavonols, flavanols, flavones, isoflavones, flavanones, catechins, anthocyanins, and anthocyanidins. These compounds exert many biological effects including immunomodulatory, anti-inflammatory and antioxidant activity. Antioxidant activity is greatly enhanced by the presence of vitamin C. Quercetin is the most abundant dietary flavonol, is a potent antioxidant and also directly inhibits expression of CYP1A1, a cytochrome P450 enzyme involved in toxins metabolism, with resultant decrease in DNA adduct formation. Elevated CYP1A1 activity has been linked to increased lung cancer risk in smokers. Several studies have found an inverse relationship between intake of foods containing quercetin and lung cancer risk, depending especially on CYP1A1 genotype (38).

**Curcuminoids.** Curcuminoids are polyphenolic pigments present in the spice turmeric which is derived from the rhizomes of *Curcuma longa*. Curcumin is the principal curcuminoid in turmeric and is a potent anti-inflammatory and chemopreventive agent. Curcumin inhibits NF-κB-dependent gene transcription, induces apoptosis in a variety of cancer cell lines and inhibits VEGF-mediated angiogenesis in human intestinal endothelial cells. Anti-cancer activity has been demonstrated in several animal models. Robust preclinical data and an excellent safety profile has led curcumin into phase I and II clinical trials to test its potential chemopreventive activity in human colon cancer. Results are awaited.

### 7. Cancer Survivors

A survivor is defined as a person diagnosed with cancer “from the time of diagnosis and for the balance of life”; this definition also includes family, friends, and caregivers. Nearly 14.5 million Americans were cancer survivors in 2014, and 64% of them were long term survivors (diagnosed more than five years before). It is estimated that by January 2024, the population of US cancer survivors will increase to almost 19 million. Given the increasing number of long-term survivors, and the possibility of competing causes of morbidity and mortality in this population, there is an increasing amount of literature addressing the role of lifestyle behaviours in the survivor population. Epidemiological and interventional studies evaluating the engagement with and promotion of healthy eating, weight control, and physical activity have been published, suggesting that lifestyle behaviours may be important to counter some of the adverse effects of cancer treatments and disease recurrence itself, while improving overall health outcomes. Lifestyle interventions are important aspects of survivorship care, as cohort studies have suggested that engagement in physical activity or adherence to a healthy diet may impact on overall quality of life as well as on disease-specific and overall health outcomes in certain tumour types (39).

### 8. Conclusions

Panelists of the second WCRF/AICR expert report reviewed all available literature on the topic and concluded that about 40% of all cancers are linked to poor diet, physical inactivity and excessive body weight. In the previous report, smoking had been judged responsible for approximately another 30% of all cancer deaths (2). That is, environmental factors prevail in
the aetiology of cancers, and inherited genetic factors cannot be accountable to any significant extent for the current growing incidence of cancer.

The second expert report recommendations include:
- maintaining a body mass index of between 21 and 23 (until now, the standard recommended range has been 18.5 to 24.5)
- exercising moderately
- limiting consumption of alcohol, energy-dense foods and refined carbohydrates
- avoiding sugary beverages
- increasing intake of vegetables and fruit to at least five portions per day
- increasing intake of whole cereals (mainly in an unprocessed form) and legumes
- consuming fast foods sparingly, if at all
- limiting intake of salty and sodium-processed foods to less than 5 g of salt or 2 g of sodium per day
- limiting consumption of red meats and avoiding processed meats
- after treatment, cancer survivors should follow these recommendations for cancer prevention

The panel conclusions are enormously important, as they bring a new level of responsibility to policymakers, public health officials, food industry, researchers, healthcare practitioners, media, communities and individuals into developing effective policies, programmes and practices aimed at effective primary cancer prevention through radical modification of the environment and lifestyle habits.

9. Summary

The number of cancer diagnoses is increasing throughout the world. Despite the considerable progress achieved in early detection and effective therapy of cancer, the war is far from being won. Instead, we are facing a real global cancer epidemic. It is estimated that in 2030 13 to 17 million deaths will occur from neoplastic diseases. Although the pathogenesis of cancer is multifactorial, with genetic predisposition playing a prominent role, there is consolidated evidence that environmental factors may be equally important in promoting cancer genesis. Since it is becoming increasingly clear that at least two-thirds of all cancers may be prevented by lifestyle modifications, physical activity, proper diet and maintenance of a healthy weight, efforts to improve primary cancer prevention appear imperative to change the current growing trends. Evidence is accumulating that healthy diet and appropriate nutritional interventions may significantly contribute to this aim.

10. References