

Module 26.5

Nutrition in 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;
- While there is no evidence that intake of non-physiologic doses of vitamin supplements would prevent an array of conditions attributable to oxidative stress, correction of vitamin D deficiency is seemingly playing a major role in reducing incidence and mortality from a host of chronic conditions, including cancer.

1. Introduction

Despite the amount of resources put into discovering a genetic origin for cancer, epidemiological and experimental research keep strengthening the notion that cancer is a disease largely caused by environmental factors. Classic genetics alone cannot explain the diversity of phenotypes within a population. Nor does classic genetics explain how, despite identical DNA sequences, monozygotic twins and cloned animals have different phenotypes and show different susceptibilities to diseases. Even genetic susceptibility to cancer due to genetic polymorphisms cannot have changed 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 it 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 will 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 imperative to consistently redirect public health policies, government programs and research funding from cancer treatment and diagnosis to primary cancer prevention if we want to significantly reduce these 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 is, in fact, 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).

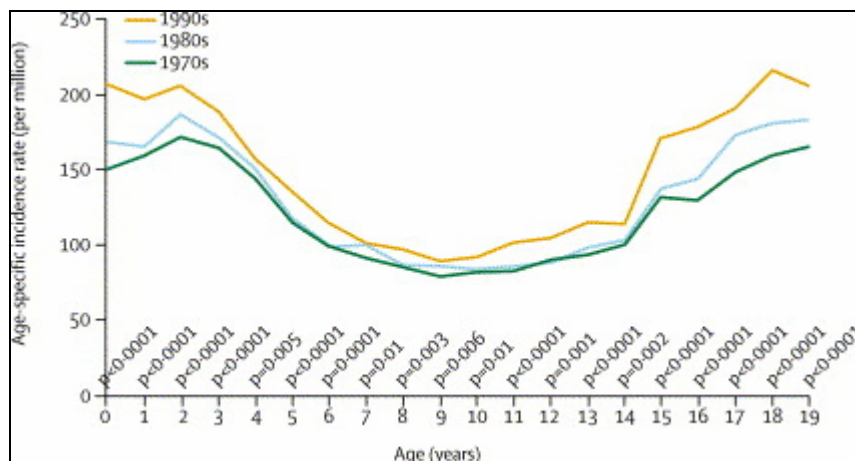


Figure 1. Age-specific incidence rates of cancer in children and adolescents in Europe values test difference between first and last decade (from Steliarova-Foucher E. *et al*, *Lancet* 2004, reproduced with permission)

Concomitantly, the economic burden of cancer is substantially increasing: 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 is 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, intervention 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.

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 1990’s 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 (7), we can estimate that over 4 million people could have been spared the tragedy of cancer by the very feasible approach of modified eating, weight control and exercise as 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. Such a task can be accomplished through reorientation of public health priorities from treatment and diagnosis to primary prevention, if the goal of comprehensive cancer control through reduction of cancer burden and suffering is to be achieved.

3.1 Cancer and the environment

For decades, research has been aimed at the genetics of cancer to find solutions to the cancer riddle. The discovery of oncogenes, tumor suppressor, DNA repair and cancer susceptibility genes has led some to conclude that the genesis of cancer 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 responsible for repairing DNA replication mistakes. This ability varies considerably among individuals because of the variation of the regulating polymorphic genes in the population 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 over time within countries and populations, e.g., 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 populations 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 play 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 (8).

Similarly, stomach cancer mortality in migrants from 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, in a few years, to equal that of the host countries (9).

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 among 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 (10), in the development of testicular cancer.

Another important study 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 decreased by 5% and 8% for immigrant men and women, respectively, compared with native Swedes (11). 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" (12).

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 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-term pregnancy and early postnatal life before trying to alter diets and behaviours of a wider population 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 was 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. Among 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 (13). 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 in the estimate of being 14 years younger in chronological age and was significantly greater than that expected from each individual risk factor, indicating that health behaviours act synergistically on pathways implicated in maintenance of proper biological functions. Along the same lines are the results of a longitudinal study conducted on European elderly 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 (14). The more the healthy behaviours were adopted by individuals, the lower the risk of cancer- specific mortality (Table 1).

Table 1. Cox Proportional Hazard Ratios and Population-Attributable Risks of the Combined Diet and Lifestyle Factors for 10-Year Cancer-Specific Mortality in Elderly Europeans (adapted from Knoops KT *et al*, JAMA 2004)

	Number of protective factors			
	0-1	2	3	4
Cancer Mortality	(n=246)	(n=702)	(n=954)	(n=437)
HR (95% CI)	1.00	0.62(0.51-0.75)	0.42 (0.28-0.62)	0.31 (0.19-0.50)
PAR (%)		14	38	60

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 intervention study, and the number of years an individual needs to maintain such a lifestyle to realize a benefit is unknown. However, the notion that adopting a healthy diet rich in fruit and vegetables, moderate alcohol consumption, being not physically inactive and non-smoking are associated with substantial lower mortality rate, even in old age, may encourage behavioural change at the population level.

4. Results from the second 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 origin of these discrepancies are multifactorial, and reflect the ample variations in foods constituents according to soil status, seasonality, storage conditions, transportation, processing and preparation, as well as 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– in both normal and cancer cells, hence evaluation of the overall impact of the thousands of dietary constituents taken with foods, is a massive task.

Given these premises, a 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).

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 the presence of confounder 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 compared to non vegetarians, colorectal cancer incidence is significantly higher in vegetarians compared to meat eaters (15). Since vegetarians are likely to consume a diet high in fiber, this adds new uncertainties to the assessment of the true value of dietary fiber 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 polymorphisms in the glutathione S-transferase (GST) family of metabolising enzymes are a factor in individual susceptibility to aflatoxin-induced hepatocarcinogenesis, since they may regulate an individual's ability to metabolize the ultimate carcinogen of aflatoxins (16);
- Non starchy vegetables and fruits probably protect against upper aerodigestive tract (mouth, pharynx, larynx, oesophagus and stomach) cancer. While the majority of studies show decreased risk of these cancers with increased intake of fruits 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, most countries have adopted national recommendations for consumption of five or more servings per day of fruits and vegetables;
- There is a significant inverse association between fruit consumption and lung cancer risk in both smokers and nonsmokers, while high vegetable intake significantly decreases lung cancer risk in current smokers (17). 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);
- Red meat and processed meat (meat preserved by smoking, curing, salting, or by the addition of preservatives) is a cause of colorectal cancer. Cooking meat at high temperatures (i.e., frying, grilling, and barbecuing) induces heterocyclic amines formation, and broiling and charbroiling meat or fish over direct flame leads to the production of polycyclic aromatic hydrocarbons. These compounds however, are ubiquitous in the diet, and we should be aware that oils, fats, cereals and vegetables are their major sources. Processed meat may also 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 nitrites or nitrates; they are recognized carcinogens. Finally, haem iron present in red meat has been shown to catalyse formation of *N*-nitroso compounds in the intestine. In any case, most epidemiological data linking red meat to colon cancer risk relate to the way meat is cooked and preserved, rather than to meat itself;

- Milk and more significantly dietary calcium (from dairy, vegetables, nuts, pulses and fish or meat cooked on the bone) protects from colorectal cancer. Total cheese may increase colon cancer risk. 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 on 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 never used hormone replacement therapy (18);
- Excessive salt and sodium intake can increase 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 (19). 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 (20). Polymorphisms and mutations in ALDH and ADH may increase individual risk of contracting cancers of the esophagus, upper aerodigestive tract and colorectum associated with alcohol

consumption, due to acetaldehyde overexposure (ref 21-24). Ethanol is also oxidated through catalase and cytochrome P450 2E1 pathways. Not only ethanol is a substrate of CYP2E1, but also a potent inducer of this enzyme, thereby increasing oxidative stress and 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 postmenopausal 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)-I and IGF-binding proteins, accumulation of environmental chemical carcinogens and sequestration of vitamin D 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 (ref 25). Although the number of overweight and obese adults is higher in the 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;

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, pesticides residues and drugs given to animals. In addition, chemical contaminants may be formed during food preparation or find their way into foods during industrial processing and packaging. The majority of these substances have never been tested for carcinogenicity. Food can also be contaminated by naturally occurring carcinogens such as mycotoxins from mold growth, and aflatoxin is a definite cause of liver cancer risk, 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, 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 of water. 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 formation of acrylamide. Acrylamide levels in food vary widely depending on the manufacturer, the cooking time, 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 is approximately 750 microgram/kg and 330 microgram/kg, respectively, although it may reach concentrations up to ten times higher (26). 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, 2–3 greater than those of adults, based on average body weight ratios (ref 26). Epidemiological studies, conducted so far generally do not support a role for dietary acrylamide as a risk factor for developing endometrial, ovarian, breast, colorectal or prostate cancer. When haemoglobin adducts of acrylamide were used as biomarkers of exposure, however, a positive association was seen between acrylamide-hemoglobin levels and estrogen receptor positive breast cancer in post-menopausal women (27). 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, 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 on 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. Carotenoids-

rich foods include carrots, apricot, peaches, cantaloupe, sweet potatoes, winter squash, kale, spinach, romaine lettuce and broccoli. Consuming five or more servings of fruits 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 that high dose synthetic beta-carotene supplementation in current smokers increases lung cancer risk and lung cancer death (28).

Isothiocyanates. These sulphur-containing phytochemicals occur naturally as glucosinolate conjugates in cruciferous vegetables and are released through hydrolysis by the enzyme myrosinase after plant cell rupture. Isothiocyanates are found in cruciferous vegetables such as broccoli, cauliflower, kale, turnips, collards, Brussels sprouts, cabbage, radish, turnip and watercress, and are responsible for the typical flavour 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 cause accumulation of 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 epidemiologic literature through 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 high intake of cruciferous vegetables, compared to those with low intake (29). 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 cauliflowers, significantly reduced risk of aggressive prostate cancer (30). 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 TGF β 1, EGF and insulin signalling pathways in human prostate gland, each of which is associated with prostate carcinogenesis (31). Perturbation of signalling pathways is influenced by *GSTM1* genotype. Additional epidemiological evidence points further toward a protective role of cruciferous vegetables against gastric, colorectal, ovarian and bladder cancer. Because of a gene-diet interaction, future studies need to investigate association with homozygous

deletion of GSTM1 and GSTT1 to gather clearer knowledge concerning the potential role of isothiocyanates in cancer prevention.

Flavonoids. Flavonoids are polyphenolic compounds ubiquitously found in plants and responsible for their pigmentation. Flavonoids are categorized according to chemical structure in 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 increase lung cancer risk in smokers. Several studies have found an inverse relationship between intake of foods containing quercetin and lung cancer risk, especially depending on CYP1A1 genotype (32).

Curcuminoids. Curcuminoids are polyphenolic pigments present in the spice Turmeric 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- κ B -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 awaiting.

Vitamin D. Although the WCRF review concluded that there is no evidence that vitamin supplements help prevent cancer, the role of vitamin D in cancer prevention deserves further comment. Vitamin D is available through solar ultraviolet (UV)-B radiation (the major source), dietary intake (from cod liver oil, salmon, tuna, mackerel, sardines, fortified milk, eggs) or supplements. A plethora of ecologic and experimental studies have consistently shown that sunlight exposure and increased vitamin D intake are associated with a reduced incidence of many types of cancer, including those of the colorectum, breast, pancreas, esophagus and ovary, and with reduced mortality from these cancers. A well-designed study conducted by Giovannucci *et al.* examined vitamin D exposure and cancer incidence in 47,800 men in the Health Professionals Follow-Up Study cohort. Results showed that an increment of 25 nmol/L in predicted 25-hydroxyvitamin D (25(OH)D) level was associated with a 17% reduction in total cancer incidence, a 29% reduction in total cancer mortality, and a 45% reduction in digestive-system cancer mortality (33). Grant *et al* analysed geographic gradients in mortality rates for a number of cancers in the U.S. (e.g., rates are approximately twice as high in the northeast compared with the southwest) and determined how many types of cancer were affected by solar radiation and how many premature deaths from cancer occurred due to insufficient UV-B radiation. They concluded that there were 18 anatomic sites of cancer that were inversely associated with U-VB irradiance, and that in the U.S. every year 17.000 to 23.000 individuals died prematurely from cancer due to

insufficient UV-B and vitamin D (34.). Autier and Gandin conducted a meta-analysis of 18 randomized trials including 57 311 participants, on the impact of vitamin D supplementation on any major chronic condition such as cancer, cardiovascular disease and diabetes. Daily doses of vitamin D supplements in the trials varied from 300 to 2000 International Unit (IU). The meta-analysis concluded that individuals who were randomized to vitamin D had a statistically significant 7% reduction in mortality from any cause. The reduction was 8% for studies for which the intervention was at least 3 years for those studies with a placebo control group (35). Results from trials of vitamin D appear to be in contrast to previous studies of micronutrients, including vitamin E and beta carotene, which showed no benefits on mortality and perhaps even adverse effects. Proposed benefits of beta carotene and vitamin E were premised on the concept that providing a nonphysiologic dose of a single "antioxidant" would prevent an array of conditions attributable to oxidative stress. In contrast, by increasing vitamin D intake, we may be correcting a deficiency caused primarily by a lack of the natural source of vitamin D, i.e., sun exposure. During exposure to solar UVB radiation, 7-dehydrocholesterol in the skin is converted to vitamin D₃. Vitamin D in the circulation is transported to the liver, where it is converted to 25(OH)D, the major circulating form used to determine vitamin D status. This form of vitamin D is biologically inactive and must be converted in the kidneys to the biologically active form, 1,25-dihydroxyvitamin D (1,25(OH)₂D). Most tissues and cells in the body have a vitamin D receptor and several possess the enzymatic machinery to convert 25(OH)D, to the active form, 1,25(OH)₂D. The rationale for the protective effects of vitamin D lies in its role as a nuclear transcription factor that regulates cell growth, differentiation, apoptosis, angiogenesis, immune function and a wide range of cellular mechanisms central to the development of cancer. Serum levels of 25(OH)D are below the recommended levels for a large portion of the general adult population and in most minorities. Vitamin D deficiency is defined by most experts as a 25(OH)D level of less than 50 nmol per litre , and the most effective serum concentrations are seen above 75 nmol/L with maximal effects seen at between 90 and 100 nmol/L (36). Vitamin D inadequacy has been reported in approximately 36% of otherwise healthy young adults and up to 57% of general medicine inpatients in the United States and in even higher percentages in Europe (37). One of the reasons for the prevalence of vitamin D insufficiency lies in the widespread use of sunscreens and in the practice of sun-avoidance. In addition, actual recommendations published in 1997 by the Institute of Medicine (IOM) indicate vitamin D adequate intake (AI) ranging from 200 to 600 IU/day, while a tolerable upper intake level (UL) has been set at 2000 IU/day for adults. Data from recent trials show that even these levels are insufficient to achieve protection from cancer and many other diseases, and point to an urgent need for revision of current recommendations to reduce global cancer burden worldwide.

7. Conclusions

Panellists of the second expert report have 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 was judged responsible for approximately another 30% of all cancer deaths (2). Environmental factors, therefore, are

the most important aetiological influences on cancer risk. Although genetic factors have some influence, they cannot account, 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 fruits 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 confer a clear responsibility on policymakers, public health officials, food industry, researchers, healthcare practitioners, media, communities and individuals for developing effective policies, programs and practices aimed at effective primary cancer prevention through radical modification of the environment, lifestyle habits and diet.

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Short summary of the module

Cancer incidence is increasing throughout the world. Despite considerable progress achieved in early detection and effective cancer treatment, 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 disease. Although the pathogenesis of cancer is multifactorial, there is consolidated evidence that environmental factors play a major role. Since it is becoming increasingly clear that almost 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 modify the actual growing trends. Evidence is accumulating that healthy diet and appropriate nutritional interventions may significantly contribute to this aim.