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WHAT TO EAT TO REDUCE CANCER RISK?

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ABSTRACT – *During medical consultation patients frequently ask what to eat in order to prevent cancer. Even though there are still some controversies, some rules are easy to perform and evidence based. Lower intake of red and processed meats and salt, and higher intakes of fruits, vegetables, and whole-grain foods are related to reduced risk of cancer. Red and processed meats increase the risk of colorectal cancer. Diets rich in high-calorie foods, such as fatty and sugary foods, may lead to increased calories intake, thereby promoting obesity and leading to an increased risk of cancer. Sugary drinks are also related to an increased risk of pancreatic cancer. There is evidence that high intakes of fruit and vegetables may reduce the risk of cancers of the aero-digestive tract. Dietary fibre protects against colorectal cancer is convincing. A healthy diet can improve overall survival after diagnosis of breast and colorectal cancers. Patients should be told that a healthy diet is very important in childhood, adolescence, and early adulthood when the rapidly developing sensitive tissues are particularly susceptible to carcinogenesis. The possibility that diet could also epigenetically change cancer risk of future generations could be a way to improve adherence to a healthy diet.*

KEY WORDS: *Diet, Nutrition, Cancer, Prevention, Counseling.*

INTRODUCTION

Typical diet may provide more than 25,000 bioactive food constituents, and the amounts of bioactive components within a particular food may vary widely. Each bioactive food constituent has the potential to modify multiple aspects of the cancer process, alone or in combination with several micronutrients, and the quantity, timing, and duration of exposure modulate the cell response. Thus, it is not possible to ascribe a causal effect to specific compounds; it is more likely that the effect results from a combination of influences on several pathways involved in carcinogenesis. Diet may influence cellular processes and lead to the accumulation of the hallmarks of cancer cells: self-sufficiency in growth signals, insensitivity to anti-growth signals, limitless replicative potential, evasion of apoptosis, sustained angiogenesis, reprogramming of energy metabolism, evasion of immune destruction, tissue evasion and metastasis[1-2].

REDUCE THE AMOUNT OF CALORIES INTRODUCED, IF OVERWEIGHT OR OBESE, IN ORDER TO REACH THE IDEAL BODY WEIGHT

The first rule is to reduce the amount of calories introduced, if overweight or obese, in order to reach or to keep the body weight as close to the ideal as possible.

This is the most evidence based and most important preventive rule. At the same time, it is the most difficult to achieve**.** Once an individual becomes obese, it is difficult to lose weight and keep

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it off, so it is fundamental to prevent any excessive increase of weight from the beginning. Calorie restriction (CR) is the most effective and reproducible intervention for increasing lifespan in a variety of animal species, including mammals. CR is also the most potent, broadly acting cancer-prevention regimen in experimental carcinogenesis models[3].

The biological mechanisms linking adiposity and cancer risk include hyper-insulinaemia and insulin resistance, up-regulation of insulin-like growth factors (IGF-1), modification of the metabolism of sex hormones, chronic inflammation, changes in production of adipokines and vascular growth factors by adipose tissue, oxidative stress, and alterations in immune function.

LIMIT FOODS HIGH IN SUGAR OR FAT (HIGH-CALORIE FOODS)

Energy-dense diets are widely used in the western world because of taste and convenience. Together with sugary drinks, they are responsible for a great part of the excessive weight increase. These foods increase cancer risk also because they contain less fibre and they are usually high in fats, processed starch, and added sugars.

REDUCE THE AMOUNT OF SUGARS, AVOID SUGARY DRINKS

Diets high in sugars may promote carcinogenesis by increasing insulin production, increasing oxidative stress or promoting weight gain. In metabolic syndrome, foods rich in sugars are likely to interfere with levels of blood glucose and/or triglycerides, either directly or through insulin and other hormones, while sugar-sweetened soft drinks play a role in the development of obesity[4].

REDUCE TE AMOUNT OF READ MEAT AND AVOID PROCESSED MEAT

Many nitroso compounds contained in red and processed meat are mutagenic and potentially carcinogenic. Haem iron, which is abundant in red meat but not in white meat, promotes colorectal carcinogenesis through its catalytic activity in the formation of nitroso compounds and lipid oxidation end products, such as 4-hydroxynonenal[5].

In processed red meat, haem iron is nitrosylated, because curing salt contains nitrate or nitrite. There is evidence that nitrosylated haem iron promotes carcinogenesis at doses 5–6 times lower than non-nitrosylated haem iron.

Calcium salts, chlorophyll, vitamin C, and several polyphenols may reduce the deleterious effects of haem iron, so it can speculated that eating vegetables too, can attenuate the cancerogenic risk of red and processed meats.

LIMIT FOODS HIGH IN SALT

Sodium chloride is a food preservative used for increasing the safety and shelf life of processed foods. In animal experiments, salt intake facilitates gastric colonisation by *Helicobacter pylori*, one of the main predisposing factors for stomach cancer development, and induces mucosal damage, potentially leading to chronic atrophic gastritis. Salt intake may also promote or enhance the effect of nitroso compounds and other carcinogens[6].

AVOID THE PARTS OF MEATS COOKED AT HIGH TEMPERATURES FOR A LONG TIME, OR EXPOSED TO A DIRECT FLAME

Heterocyclic amines and polycyclic aromatic hydrocarbons are other potential carcinogens that are formed in meats cooked at high temperatures for a long time, or exposed to a direct flame. This is not limited to red and processed meats. Various single-nucleotide polymorphisms involved in the metabolism of these potential carcinogens may modulate the association of carcinogens formed in meat with cancer risk[7].

REDUCE TRANS FATTY ACIDS

Trans fatty acids could be associated with an increased risk of neoplasms, like breast cancer[8,9].

EAT MOSTLY WHOLE GRAINS, PULSES, VEGETABLES AND FRUITS

A potentially protective effect of fruits and vegetables against cancer is supported by evidence from earlier case–control studies, but subsequent data from prospective studies indicate that the association may be restricted to specific cancers and may be weaker than previously observed for some tumours.

This lack of clarity may result from the differences in what is considered vegetarian diets, food intake and lifestyle. In addition to reduced consumption of animal products, vegetarians eat less refined grains, added fats, sweets, snacks foods, and caloric beverages than non vegetarians and increased

amounts of a wide variety of plant foods. Such a pattern might be expected to reduce hyperinsulinemia. The Body Mass Index may be one mediator of the dietary effects and vegetarians, mostly vegans, tend to be leaner. Plant-based diet is associated with lower circulating levels of total IGF-I and higher levels of IGFBP-I and IGFBP-2 compared with a meat-eating, which are oncoprotective[10,11].

Among the 69,120 participants of the Adventist Health Study-2[12] vegan diets showed statistically significant protection for most female-specific cancers (HR=0.66; 95%CI: 0.47, 0.92) and for overall cancer incidence (HR=0.84; 95%CI: 0.72, 0.99) in both genders combined. Vegetarian diet reduces typically cancers of the gastrointestinal tract (HR=0.76; 95%CI: 0.63, 0.90) and the overall reduced (?) cancer risk among vegetarians compared to non-vegetarians is statistically significant (HR=0.92; 95%CI: 0.85, 0.99) for both genders combined. The adjusted hazard ratios (HRs) in all vegetarians combined vs. non-vegetarians is 0.78 (95% CI, 0.64-0.95) for all colorectal cancers, 0.81 (95% CI, 0.65-1.00) for colon cancer, and 0.71 (95% CI, 0.47-1.06) for rectal cancer.

The adjusted HR for colorectal cancer in vegans is 0.84 (95% CI, 0.59-1.19); in lacto-ovo vegetarians, 0.82 (95% CI, 0.65-1.02); in pesco-vegetarians, 0.57 (95% CI, 0.40-0.82); and in semi-vegetarians, 0.92 (95% CI, 0.62-1.37) compared with non-vegetarians[13].

Low intake of fruits and vegetables is related with the development of cancers of the respiratory and upper digestive tracts[14,15].

The evidence of an association between fruits and vegetables and colorectal cancer has been judged as "limited–suggestive" in the 2007 WCRF/AICR report. Evidence for an inverse association has been reported in the more recent WCRF/AICR update, in which a non-linear relationship has been observed, indicating that the benefit from an increase in fruit and vegetable consumption would be limited to people with the lowest intake levels, and that no substantial benefit would occur in people who already have a high intake of high fruits and vegetables. Not included in this update the large NIH-AARP American cohort study which more recently has reported an inverse association between vegetable intake and colon cancer, but no association between fruits and colon cancer[16].

EAT VEGETABLES HIGH IN FIBER

Dietary fiber from plant foods stimulates bacterial anaerobic fermentation in the large bowel, leading to the production of short-chain fatty acids: acetate, propionate, and butyrate. In cell lines, butyrate reduces cell proliferation and induces apoptosis.

In a meta-analysis of prospective studies[17], there has been an inverse association between dietary fiber intake and breast cancer risk. The summary RR per 10 g/day of dietary fiber is 0.95 (95% CI 0.91-0.98). In stratified analyses, the inverse association has been only observed among studies with a large range (≥13 g/day) or high level of intake (≥25 g/day).

Two dietary intervention studies among women diagnosed with breast cancer, the Women's Healthy Eating and Living Trial (WHEL) and the Women's Intervention Nutrition Study (WINS), have found that dietary interventions among breast cancer survivors without weight loss or increase in physical activity do not improve breast cancer prognosis. WHEL have focused on a plant-based dietary pattern that included a reduction in dietary fat, while WINS have focused on reduced dietary fat intake. Secondary analyses in WHEL have showed that the dietary intervention pattern have been associated with a reduced risk of second breast cancer events among women with early-stage breast cancer who reported no hot flashes at baseline, and that higher vegetable intake has been associated with reduced breast cancer recurrence in tamoxifen users[18,19].

The evidence for a protective role of a dietary fibre on colorectal cancer in recent publications is stronger and there is some evidence that it could be even stronger for fibres from cereals. Fibres may protect against colorectal cancer by reducing the contact between the intestinal contents and the mucosa, and may interfere with the enterohepatic circulation of oestrogens. Some studies have shown a reductions in circulating oestrogen and androstenedione levels through high fibre intake in premenopausal women[20].

In post menopausal women dietary fibre intake is inversely associated with E1 and E2. There is a 22% and 17% decrease (2Ptrend = 0.023 and 0.045) among subjects in the highest quintile of intake compared with the lowest. Fitting dietary fibre together with soluble and insoluble non-starch polysaccharides (NSP) has shown a much greater decrease in E1 and E2 (47% and 41%, respectively).

Surprisingly, increased soluble NSP intake has shown an augmentation in E1 and E2 (64% and 69%, respectively). Avocado and grapefruit, have shown a significant positive associations with E1 (2Ptrend = 0.029 and 0.015, respectively): they increased oestrogen levels[21].

This is controversial, in experimental studies in mice, soluble fibre reduced mammary tumour growth, angiogenesis and metastasis[22].

Fibre-rich foods are important sources of phyto-oestrogens, oestrogen-like plant compounds

that may interact with and modulate the activity of oestrogen receptors, alpha and beta, thereby modulating the risk of hormone-dependent cancers (especially breast cancer)[23].

Polyphenols from plant foods have multiple biological effects, including scavenging of oxidative agents, anti-inflammatory and detoxifying actions, inhibition of platelet aggregation, and antimicrobial activity[24].

Isothiocyanates (ITCs), the majority of which occur in plants, especially in cruciferous vegetables, have cancer-preventive activity[25].

INCREASE THE AMOUNT OF FOODS THAT CONTAIN CANCER PREVENTI SUBSTANCES

Diallyl disulphide from garlic and other allium vegetables, and sulphoraphane, a glucosinolate from cruciferous vegetables, can behave as histone deacetylase (HDAC) inhibitors and act to maintain DNA stability or enhance transcription. HDAC inhibitors disrupt the cell cycle and/or induce apoptosis via de-repression of genes such as P21 and BAX, and cancer cells appear to be more sensitive[26].

Naturally occurring bioactive compounds such as curcumin, resveratrol, and isothiocyanates have potential antioxidant and/or anti-inflammatory and anti-carcinogenic activities.

VITAMINS AND MINERALS SHOUD COME FROM A BALANCED DIET, NOT FROM SUPPLEMENTS

Vitamins and minerals such as carotenoids, folate, vitamins C, D, E and B6, selenium, and phytochemicals might reduce cancer risk through preventing oxidative damage, inhibiting cell proliferation, inducing cell-cycle arrest, maintaining DNA methylation, and/or modulating steroid hormone concentrations and hormonal metabolism (e.g., via phyto-oestrogen contained in pulses)[27].

FOLLOW THE CANCER PREVENTIVE NUTRITION GUIDELINES MORE STRICTLY IN CRITICAL GROWTH PERIODS, LIKE PREGNANCY AND PUBERTY

Early life, adiposity rebound, and puberty represent critical growth periods when food choices could have long-term relevance for cancer risk. The induction of changes to the phenotype of the offspring in response to the prenatal environment that persist throughout the lifespan, implies stable changes to gene transcription resulting in altered activities of metabolic pathways and homeostatic control processes, and in differences in the structure of tissues.

Higher birth weight, which reflects a more abundant prenatal environment, is associated with increased risk of cancer, in particular breast cancer and childhood leukaemia. Foetal programming effects occur over the usual range of birth weights rather than being the result of pathological states such as intrauterine growth retardation or macrosomy. These developmental responses to environmental stimuli through developmental plasticity, induce adaptations to the phenotype of the foetus which predicts the postnatal environment with the aim of conferring a survival advantage. A mismatch between the predicted environment and that which the offspring experiences after birth results in a disadvantage that in humans leads to increased risk of disease. Prenatal nutrition on health in adulthood can be transmitted to more than one subsequent generation[28].

Risk of breast cancer is increased in individuals with higher birth weight[29-36].

A meta-analysis supports the overall conclusion that risk of breast cancer is increased in individuals with higher birth weight. Higher birth weight has been associated with 12% increase in relative risk of breast cancer, while higher birth length was associated with 28% increased risk of disease[37].

High birth weight or compensatory mammary growth led to breast cancer susceptibility and it increases mammary tumour incidence in rats[38-40].

BE AWARE THAT EMBRYO NUTRITION COULD INDUCE EPIGENETIC CHANGES

The induced epigenetic changes can be permissive for altered gene expression and hence determine the interaction between an organism and its environment over the life course and, in turn, determine whether the increased risk due to the early life environment becomes a cancer or other diseases in later life. However, this is an emerging field of research.

Phenotypes induced by variations in maternal nutrition during pregnancy are subtle and could only become clinically apparent after the neonatal period in childhood or adulthood. Nutrition in early life can induce both hypomethylation and hypermethylation of specific CpG dinucleotides. Prenatal epigenetically-induced increased cancer risk is associated with global hypomethylation of the genome that reflects the global decline in DNA methylation associated with increasing age related to a reduction in Dnmt1 activity which, in turn, may induce expression of oncogenes such as c-*Myc* and c-N-*ras*[41].

Table 1. What and how to eat to reduce cancer.

- Reduce the amount of calories introduced, if overweight or obese, in order to reach the ideal body weight
- Limit foods high in sugar or fat (high-calorie foods)
- Reduce the amount of sugars, avoid sugary drinks
- Reduce the amount of read meat and avoid processed meat
- Limit foods high in salt
- Avoid the parts of meats cooked at high temperatures for a long time, or exposed to a direct flame
- Reduce food containing trans fatty acids
- Eat mostly whole grains, pulses, vegetables and fruits
- Eat vegetables high in fiber
- Increase the amount of foods that contain cancer preventive substances
- Introduce vitamins and minerals from a balanced diet, not from supplements
- Follow the cancer preventive nutrition guidelines more strictly in critical growth periods, like pregnancy and puberty
- Be aware that nutrition could also induce long lasting genetic changes

This may be accompanied by methylation *de novo* of tumour suppressor genes by increased Dnmt3a activity leading to aberrant activation of genes involved in cell proliferation and cell differentiation. A change in the epigenetic regulation of genes has been implicated as a causal mechanism in specific cancers including lung, prostate and breast cancer[42], colon cancer[43], and haemopoietic cancers[44].

Even though the cancerogenic influences of maternal nutrition on embryo future cancer development are still speculative, they are plausible. Stronger changes on embryo environment, like *In vitro* fertilisation using the intracytoplasmic sperm injection technique, are associated with increased risk of Angelman's syndrome and Beckwith-Weidemann syndrome due to loss of methylation of regulatory regions of some genes, respectively, causing dramatic alterations to the phenotype of the offspring which are evident in early life[45-47].

We do not jet know if IVF will also change cancer susceptibility in humans.

CONCLUSIONS

Even though some important aspects of diet and cancer are still controversial, patients need simple, easy to remember and to perform rules, as summarized in table 1. These rules, driven from the last version of the European Code Against Cancer, should ideally be adapted to each level of knowledge and to the changing needs. Patient must be told that an unhealthy diet could be particularly harmful in critical developmental periods like the embryo and puberty. To increase adherence, in some cases, they could consider that what they eat today could also potentially change cancer risk of future generations.

Conflict of Interests:
The Authors declare that they have no conflict of interests.

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