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Review Article

Role of nutrition in cancer

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Abstract

Cancer is a term that describes a collection of relatable diseases. Characteristic to a majority of cancers, a cell starts dividing uncontrollably and invades neighbouring tissues. Most cancers form solid tumours, except in the case of leukaemia[1].Lifestyle and dietary measures can play a vital role in the prevention of many types of cancer[2]. This paper focuses on various dietary factors that either increases/ decreases cancer risk in individuals. Further, specific nutrients as an adjunct to chemotherapeutic drugs in the treatment of cancer are evaluated for their safety, effectiveness, and reliability.

1. Introduction

Cancer is a very delicate subject, with various factors triggering the unregulated growth of cells. Broadly, cancers can be triggered by genetic, dietary and environmental factors. Statistically, only 5-10% of cancers are due to the genetic predisposition of the individual, which means 90-95% are due to environmental/dietary factors [2].Off late, people readily opt for heavily processed foods and do not pay much attention to the portion size, or the nutritional quality of their meals. Repeated intake of such heavily processed products may affect the metabolism and the growth of somatic cells. Many studies show that cancer can be easily prevented through lifestyle and diet changes [3–5].

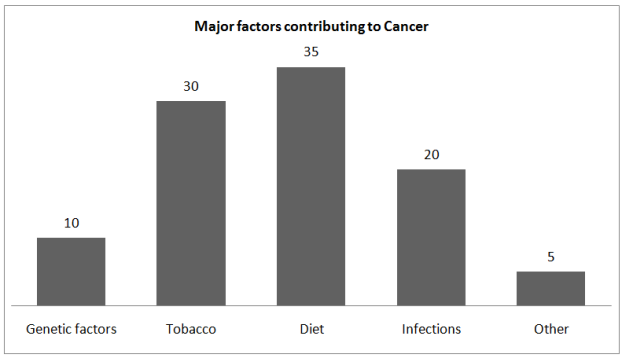

Figure 1: Major factors contributing to Cancer [2]

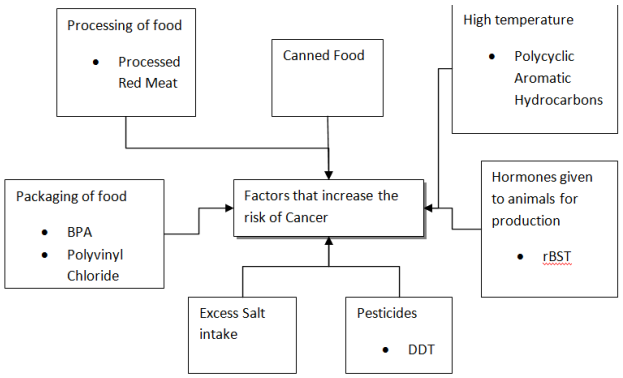

Figure 2: Factors that increase the risk of cancer

Diet often acts as a double-edged sword role in cancer risk. There are articles on the occurrence of cancer due to the excessive intake of certain foods. For instance, red meat and processed food increase the occurrence of colorectal cancer; while over processing of food leads mainly breast or stomach cancer[6]. There is also research stating that scalding hot food or drinks can also increase the risk of cancer in the oral cavity[7].On the other hand, research has shown that fruits and vegetables like cabbage and berries can respectively reduce the chance of breast and colon cancer [8,9].

There is a paucity of reviews that have compiled dietary factors together. Further, details on the therapeutic use of diet as an adjunct to cancer therapy are also lacking. Hence the focus of this review is to highlight the various dietary factors that could either lead to an increase or a decrease in cancer risk.

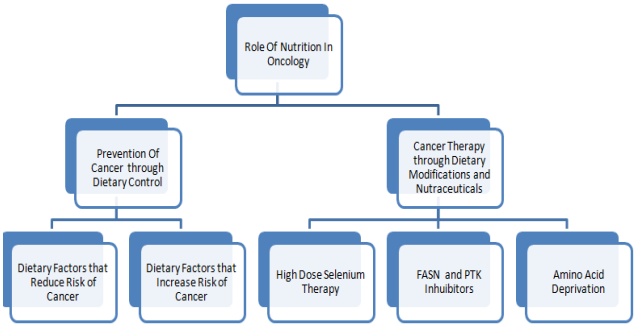

Figure 1: Role of Nutrition in Oncology

2. Dietary that decreases the risk of cancer

2.1 Fruits and vegetables

All green vegetables or plants are known to contain chlorophyll for their light capturing properties. Chlorophyll is known to be converted into pheophytin, pyro pheophytin, and pheophorbide when processed vegetable food is ingested by humans. The antimutagenic and tumoricidal potencies of these compounds were found to be effective against the mutagen, 3-methylcholanthrene (3-MC) [10]. Chlorophyll itself is involved in the reduction of carcinogenic uptake and is shown to elevate the secretion of mutagenic compounds like aflatoxin, which has been confirmed using rodent models [11,12].

In cruciferous vegetables, the presence of sulforaphane, an isothiocyanate is found to be effective in the reduction of the risk of prostate cancer. Sulforaphane is known to induce inhibition of the proliferation of prostate cancer cells and the subsequent apoptosis of the same [13–15]. It is seen that the mean content of sulforaphane in broccoli was five times more than that of cabbage. In broccoli, the florets were found to contain more sulforaphane than the leaves [16].

Brassica or Chinese cabbage consumption by the majority of the Eastern female population has been linked to a lower incidence of breast cancer, as that compared to the Western population. Animal studies showed that the cabbage have certain factors like isothiocyanates (ITC) and other glucosinolate derivatives capable of

inducing Phase II enzymes involved in detoxification [17], interact with estrogens metabolism [18–21] and reduce the estrogen level and finally, causes apoptosis of tumorigenic cells [22–25].

N. Seeram *et al*(2006) observed a relationship between the antioxidant property of berries and an increased inhibition of cell proliferation. The berry extracts were also seen to stimulate apoptosis in COX-2 expressing colon cancer cell lines. Black raspberry and strawberry extracts were shown to have the most significant pro-apoptotic effects [9].

A huge study consisting of around>5,00,000 individuals (men and women) around Europe was performed for a decade, to find out the exact relation between fruits, vegetables and cereal intake, with respect to cancer. A brief summary is as follows: There is no substantial relation between the consumption of fruits and certain cancers. (for eg., cancer of the pharynx, larynx, breast). However, it was found that the consumption of cereal fibre is proved to reduce to chance of colorectal cancer [26]. In another study, intake of fruits was beneficial for lung cancer among smokers, which may be due to the action of anti-oxidants present in the fruits that may act against the oxidative stress produced during smoking [27].

Thus the consumption of fruits and vegetables, and finding the exact element that plays a vital role in the prevention of cancer is difficult to analyse, as it depends on many factors [28]. The determination of single component effect on cancer is masked by the cumulative effect by protectors (for eg., beta-carotene, vitamin E, calcium)[29,30]. This could probably be the reason for observing a mixed association of fruits and vegetables with cancer.

2.2 Nuts and seeds

Nuts are also seen to have a role in reducing cancer risk. Although there are some studies that point out that there is no relation between the consumption of nuts and cancer, there are speculations that the regular consumption of the same can prevent tumours of the colon, rectum and prostate [31]. Potential mechanisms through which nuts can aid is through their anti-oxidant property, DNA repair mechanism, and through the supply of monounsaturated fatty acids and fibre [32,33].

Flax seed is known to be an excellent source of fibre, omega 3 fat, and lignans. The lignans are metabolized into enterodiol and enterolactone in the digestive tract[34,35]. The flaxseed lignan, as well as the mammalian metabolites, have various health benefits ranging from the prevention of breast cancer to colon cancers[35,36].

Brazil nuts are known to have a variety of nutrients ranging from polyunsaturated fats to phytochemicals that include tocopherol and squalene. Brazil nuts are known to have a great amount of selenium. It is found that a selenium supplementation is shown to reduce the incidence of prostate cancer in individuals, and especially more so when the individual has lower levels of baseline selenium levels [37]. The intake of Brazil nuts can also help prevent mammary cancer, as reported by Ip and Lisk (1994) [38].

2.3 Vitamins

(I) Folic acid and vitamin B12

Folic acid and vitamin B12 are involved in DNA synthesis and DNA methylation. Therefore, a deficiency of these factors may lead to a higher mutation rate, followed by a high risk of either stomach or skin cancer [39–41]. In the study conducted by Kana Wu *et al*(1999), there was no significant relation between folate and breast risk cancer. However, a higher risk was found in individuals who had lower levels of vitamin B 12 [42]. It was concluded that since vitamin B12 is involved in the *de novo* synthesis of methyl groups, a deficiency would result in carcinogenesis [43]. Shumin M. Zhang *et al*. (2008) conducted a randomized trial of women to find the relation between vitamin B6, vitamin B12, and folate and found that there was neither harmful nor beneficial towards cancer risks [44].

(II) Vitamin D

Vitamin D is considered to have anti-cancerous effects, and can be considered as a potent chemoprotective agent against cancer [45]. The steroidal hormone 1,25-dihydroxyvitamin D3, the active metabolite of vitamin D, is being extensively studied in its possible role in cancer treatment including prostate, breast, and pancreatic cancer [46,47]. However, the only drawback of this hormone is hypercalcaemia, and hence other analogues are studied to replace this hormone.

2.4 Antioxidants

(i) **β- Carotene:**

Beta-carotene is an antioxidant, part of a family of oxidants known as carotenoids [48].Since this compound is found in many vegetables and fruits, it was believed that high doses of beta-carotene could lead to the prevention of cancer. However, many studies showed a negative result, and in two case studies, high doses in the form of supplements were found to increase the risk of lung cancer, and a third case study showed that there was neither any harm nor benefit [49–51]. In a long-term study conducted by K. T Kelsey *et al*(1998), a large-scale experiment involving males was done to analyse the effect of β- carotene and the risk of cancer. The result showed that there was no statistically significant benefit/ harm towards malignant neoplasms when supplemented with 12 years of carotene [52]. However, the study suggests that certain micronutrients like vitamin E may be more effective in the prevention of cancer [53–55].

(ii) **Lycopene:**

Consumption of the carotenoid, lycopene is shown to reduce the risk of prostate cancer. Tomatoes are a major source of lycopene, and it has also been shown that the consumption of tomatoes has an inverse effect on the risk of cancer [56]. In a study by Peter H. Gann *et al*(1999), many such antioxidant levels were examined in male participants, and it was seen that only lycopene had consistent serum levels in relation to prostate cancer. The link between lycopene and prostate cancer is still unknown, and the exact mechanism is still under investigation. The absorption of lycopene and the bioavailability in the individual remains to be a complex mechanism depending on the food processing, lipid intake and cooking method [57].

(III) Vitamin C:

Vitamin C is known to reduce cancer risk, being present in a number of fruits and vegetables, particularly oranges, grapefruits, and peppers. Many studies have correlated a reduction in cancer risk while consuming vitamin C-rich food [58,59]. However, the intake of vitamin C supplements does not have a significant effect on reducing cancer risk [60].

2.7 Minerals:

Zinc has a big role in cellular differentiation and cell growth. The effect of zinc can be double-edged. On one hand, a deficiency of zinc can lead to an increase in prostate cancer, on the other- the presence of zinc aids in the proliferation of tumour cells. Specific tissues have a higher accumulation of zinc, and this can lead to the incidence of cancer. For example, cancerous breast cells tend to accumulate more zinc than a normal breast cell. In other tissues, there is a significant reduction of zinc concentration in the cancerous cell as compared to the normal cell [61,62].

Carcinogens have been found to increase sodium content and decrease potassium content. Sodium has been shown to increase tumour proliferation, contrary to potassium [63]. Besides the ratio of calcium and magnesium must also be delicately managed, as the deficiency of these two minerals can lead to the production of mutations in the cell, favouring DNA mutations [64].

3. Dietary factors that increase the risk of cancer

3.1 Over-eating:

Most of the studies are often based on two major concepts, which include either finding the extent of malignant effects that are brought upon through overeating, or analyzing the protective benefits of eating less. Obesity, often tied to increasing Type II diabetes as well as cardiovascular diseases risks, also plays a role in contributing towards cancer risk. The physiological levels of peptide and steroid hormones and their binding factors are mainly affected by poor metabolism due to obesity. Overeating and obesity is clearly related to a higher cancer risk and can lead to colon and rectum cancers, the cancer of the liver and cancers in the breasts of postmenopausal women [48].

There are few studies on the relation between losing weight and a reduction in risk of cancer, but it is believed that losing weight can lead to a reduction in breast cancers, and others [65]. In a study of around 7500 women participants were analysed for the effect of low-calorie intake on breast cancer risk. The conclusion is that severe calorie restriction confers to a lower incidence of breast cancer [66]. Fung T. *et al*(2003) had studied the effect of two major dietary patterns, the "prudent" and " Western" patterns on the risk of colon cancer. The "prudent" lifestyle was associated with a high intake of fruits, vegetables, and high fibre content. The "western" dietary pattern refers to a high intake of red meats, desserts, and processed foods. While no relation between prudent diets and colon cancer was found, a high risk of colon cancer was associated with a Western dietary pattern [67]. The results presented by EPIC (European Prospective Investigation into Cancer and Nutrition) showed that the consumption of red meat, processed food, high alcohol intake, abdominal obesity and a high BMI are risk factors towards colorectal cancer. Women, with high BMI, are also at risk of breast cancer [68]. Also, the energy consumed by those who frequented fast-food joints was found to be more than the low consumers [69].

3.2 Meat:

The intake of red meat is frequently associated with the risk of colon cancer. A study was conducted to test the effects of meat and vegetable fibre on a group of male participants, who had answered a detailed questionnaire about their dietary habits. It was found that again, the red meat had a significant impact on the risk of colon cancer, and no association was found between animal fat and colon cancer [70]. Another study had analysed the level of *N*-acetyltransferase (NAT) which activates several carcinogenic heterocyclic amines that form DNA adducts in the colon epithelium. The association of red meat consumption with colorectal cancer was stronger in men due to a rapid acetylation at the NAT enzyme, especially in older men (> 60 years of age) [52].

3.3 Processing of Food:

Processing of certain types of foods is known to increase the incidence of cancer. For example, the charring of meats increases the presence of carcinogens, like amino-l-methyl-6-phenylimidazo 4,5- A pyridine, found mainly in pyrolysate products of meat and fishes. This carcinogen is known to produce colon and rectal cancers in mice models [71]. It is also seen that this carcinogen acts as an "initiator", as well as an organ and lobe-specific "promoter". This suggests that the carcinogen uses inflammatory mechanisms to induce cancer in the rat ventral prostate [72].

Processed food that uses nitrates as a preservative is known to be associated with an increased risk of colon and stomach cancer [58,73]. Finally, diets with high levels of salt and sugar uptake are known to increase cancer risk levels [48].

3.4 Adulterants:

Consumers must be wary while buying fruits and vegetables. Pesticides and herbicides used to increase crop yields in farms have shown to have an effect on increasing cancer risks. Organochlorines, creosote, and sulfate are found to be carcinogenic. The well-known organochlorine, DDT is a tumour promoter [74].

Argemone oil and butter yellow are common adulterants of edible oil and has seen to increase the occurrence of gallbladder carcinoma [75].There are also cases wherein injectable dyes are used for artificial ripening of fruits like watermelon and mangoes. These dyes are reported to contain calcium carbide and formalin and are known to be toxic and carcinogenic. Another adulterant is "metanil-yellow", used to dye pulses and turmeric powder. This dye is a "coal-tar dye" which is also found to be carcinogenic towards hepatic cells [76].

4. Nutrition as an adjuvant for the treatment of cancer

Diet can act as an adjuvant to cancer treatment. For example,fermented soy products which have a high content of isoflavones has been reported to have anti-estrogenic activity. Consumption of such products has the decreased incidence of mortality and recurrence of breast cancer [77]. High dose Selenium Therapy and the FASN therapy are used to treat cancer.

4.1 Synergistic effect- cancer therapeutic agent vs. nutrition

Selenium (Se) is an important mineral that is required for many cellular processes [78], and Se is also seen to have a preventive function of some forms of cancer, mainly because it is a component of several selenoproteins [79,80]. Selenium acts on inducing apoptosis in tumour cells. The mechanism of apoptosis induction is variable depending on the structure, metabolism, and type of cell line. For eg, methyl selenol inhibits the extracellular signal-related kinase pathway activation in fibrosarcoma tumour cells [81]. Glioma and melanoma are two types of malignant tumours that cannot be treated with conventional chemotherapeutic measures. Temozolomide (TMZ) is a DNA alkylating agent that is used in the treatment of many human diseases like glioma and melanoma, TMZ, being a frontline drug often gives disappointing results. An experiment was conducted to study the effects of Se along with TMZ. The results showed a pronounced cytotoxicity against glioma and melanoma cells when TMZ was used along with Se than just TMZ alone. Also, those cells that show resistance towards TMZ were also cleared by TMZ-Se. This study demonstrates that producing complexes with Se could increase the efficiency of chemotherapeutic drugs [82].A supplementation of selenium based food products to this type of therapy could lead to a significant decrease in the incidence of carcinomas [83]. As mentioned above, nuts are a rich source of selenium and can thus be used as a supplement to this therapy and can be used as an adjuvant therapeutic agent.

Fatty Acid Synthase (FASN) is a multifunctional enzyme that is required for the endogenous synthesis of long-chain fatty acids from the precursor's acetyl- CoA and malonyl- CoA [84]. When this enzyme is blocked, human cancer cells that overexpress FASN are subjected to cytotoxicity[85]. FASN inhibition also shows a novel therapeutic agent for the treatment of multiple myelomas (MM), this was seen using the small molecular inhibitor Cerulenin. This molecule had triggered caspase- independent apoptosis in MM cell lines and resulted in the cytotoxicity of these cells [86]. The drawback of inhibiting FASN is that the enzyme triggers anorexia and weight loss in patients. This can be circumscribed by the use of epigallocatechin-3-gallate (EGCG), found in green tea. The results were found to correlate the action of EGCG from green tea, and inhibition of FASN with anti-cancerous activity, without the previously mentioned drawback [87].

5. Conclusion

From this review, it can be concluded that nutrition acts as a double-edged sword. On one hand, cruciferous vegetables like cabbage and broccoli have found to have a significant effect on reducing the chance of breast cancer. Intake of antioxidants like β-carotene and lycopene also show a reduction in chronic inflammation, which is key to cancer development. Fruits like berries,

have anti-oxidant effects, and can reduce the chances of lung cancer in smokers. On the other hand, over processed foods can lead to cancer. Besides, additives like nitrates and the intentional addition of adulterants seem to only aggravate the occurrence of cancer.

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