Cancer notes

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What is cancer?

Cancer is the uncontrolled growth of abnormal cells anywhere in the body. These abnormal cells are termed cancer cells, malignant cells, or tumor cells. These cells can infiltrate normal body tissues. Many cancers and the abnormal cells that compose the cancer tissue are further identified by the name of the tissue that the abnormal cells originated from (for example, breast cancer, lung cancer, and colorectal cancer). When damaged or unrepaired cells do not die and become cancer cells and show uncontrolled division and growth - a mass of cancer cells develop. Frequently, cancer cells can break away from this original mass of cells, travel through the blood and lymph systems, and lodge in other organs where they can again repeat the uncontrolled growth cycle. This process of cancer cells leaving an area and growing in another body area is termed metastatic spread or metastasis. For example, if breast cancer cells spread to a bone, it means that the individual has metastatic breast cancer to bone.

What are risk factors and causes of cancer?

Anything that may cause a normal body cell to develop abnormally potentially can cause cancer. Some cancer causes remain unknown while other cancers have environmental or lifestyle triggers or may develop from more than one known cause. Some may be developmentally influenced by a person's genetic makeup. Many patients develop cancer due to a combination of these factors.

RISK FACTORS

1. Heredity
2. Ionizing radiation
3. Chemical substances
4. Dietary factors – Meat, energy balance, fat, protein, alcohol, nitrates
5. Estrogens
6. Viruses
7. Stress
8. Age

1. Heredity:

A number of specific cancers have been linked to human genes and are as follows: breast, ovarian, colorectal, prostate, skin and melanoma. The higher the amount or level of cancer-causing materials a person is exposed to, the higher the chance the person will develop cancer. In addition, the people with genetic links to cancer may not develop it for similar reasons (lack of enough stimulus to make the genes function). In addition, some people may have a heightened immune response that controls or eliminates cells that are or potentially may become cancer cells.

2. Ionizing radiation:

Uranium, radon, ultraviolet rays from sunlight, radiation from alpha, beta, gamma, and X-ray-emitting sources can predispose to cancer by rupturing DNA strands, thus causing mutations.

3. Chemical substances:

Chemical substances that can cause mutations are called carcinogens. Example of carcinogens are - benzene, asbestos, nickel, cadmium, vinyl chloride, benzidine, N-nitrosamines, tobacco or cigarette smoke (contains at least 66 known potential carcinogenic chemicals and toxins).

4. Dietary factors – Meat, energy balance, fat, protein, alcohol, nitrates:

MEAT:

Meat intake has been associated with risk of digestive tract cancers. Intake of red meat and white meat known to increase the risk of colon cancer. High intake of fish sauce may be a risk factor for gastric cancer.

ENERGY BALANCE:

The relationship between body weight, body mass index, or relative body weight and site specific cancer has been found to be positively associated with the cancers of the breast, endometrium, gall bladder, and kidney. Physical inactivity, high energy intake, and large body mass are associated with increased risk of developing colon cancer in both men and women.

FAT:

A high intake of saturated fat increases the risk of prostate cancer.

PROTEIN:

Increased meat intake has been found to be associated with an increased risk of colon cancer and with advanced prostate cancer.

ALCOHOL:

Alcohol has a causal role in carcinogenesis, especially for the cancers of the mouth, pharynx and esophagus. Alcohol has an increased effect on those tissues that directly get exposed to it during its consumption, and tends to act synergistically with tobacco. Beer consumption has been associated with an increased risk for colorectal cancer.

NITRATES:

Nitrates are present in variety of foods, and the main dietary sources are vegetables and drinking water. Sodium and potassium nitrates are used in the processes of salting, pickling and curing foods. Nitrosamines are present in tobacco and tobacco smoke. Nitrosamines related to nitrates and nitrates are potent carcinogens.

5. Estrogens:

Estrogens have been given for the relief of post-menopausal symptoms and for the prevention of osteoporosis. Estrogens may play role in the production of the breast and endometrial cancer.

6. Viruses:

Viruses may act as cofactors in the development of some malignant diseases. There may be a possible role of hepatitis B virus in human primary liver cancer. Human papillomavirus and the Epstein Barr virus are considered oncogenic.

7. Stress

Stress may cause damage to the thymus gland, and the immune system and hormonal effects mediated through the hypothalamus, pituitary and adrenal cortex. This may provide the neurologic currency that converts anxiety to malignancy.

8. Age

The risk of developing colorectal cancer increases with age. The incidence is 6 times higher among persons aged 65 years and older than in comparison to persons aged 40-64 years. Increasing risk of cancer with age reflects the accumulation of critical genetic mutations.

What are cancer symptoms and signs?

Symptoms and signs of cancer depend on the type of cancer, where it is located, and/or where the cancer cells have spread. For example, breast cancer may present as a lump in the breast or as nipple discharge while metastatic breast cancer may present with symptoms of pain (if spread to bones), extreme fatigue (lungs), or seizures (brain). A few patients show no signs or symptoms until the cancer is far advanced.

Seven warning signs and/or symptoms that a cancer may be present, and which should prompt a person to seek medical attention.

1. Change in bowel or bladder habits
2. A sore throat that does not heal
3. Unusual bleeding or discharge (for example, nipple secretions or a "sore" that will not heal that oozes material)
4. Thickening or lump in the breast, testicles, or elsewhere
5. Indigestion (usually chronic) or difficulty swallowing
6. Obvious change in the size, color, shape, or thickness of a wart or mole
7. Nagging cough or hoarseness

Other signs or symptoms may include the following:

- Unexplained loss of weight or loss of appetite
- A new type of pain in the bones or other parts of the body that may be steadily worsening, or come and go, but is unlike previous pains one has had before
- Persistent fatigue, nausea, or vomiting
- Unexplained low-grade fevers with may be either persistent or come and go
- Recurring infections which will not clear with usual treatment

What are the different types of cancer?

- **Carcinoma:** Cancer that **begins in the skin or in tissues that line or cover internal organs** -- "skin, lung, colon, pancreatic, ovarian cancers," epithelial, squamous and basal cell carcinomas, melanomas, papillomas, and adenomas.
- **Sarcoma:** Cancer that begins in **bone, cartilage, fat, muscle, blood vessels, or other connective or supportive tissue** -- "bone, soft tissue cancers," osteosarcoma, synovial sarcoma, liposarcoma, angiosarcoma, rhabdosarcoma, and fibrosarcoma
- **Leukemia:** Cancer that starts in **blood-forming tissue such as the bone marrow** and causes large numbers of abnormal blood cells to be produced and enter the blood -- "leukemia".
- **Lymphoma and myeloma:** Cancers that begin in the cells of the immune system -- "lymphoma," T-cell lymphomas.

- **Central nervous system cancers:** Cancers that begin in the tissues of the brain and spinal cord -- "brain and spinal cord tumors".

The Development of Cancer (Pathogenesis)

Cancer: Initiation, Promotion, and Progression

Carcinogenesis is a multistage process. The application of a cancer-producing agent (carcinogen) does not lead to the immediate production of a tumor. There are a series of changes after the initiation step induced by the carcinogen. The subsequent stages tumor promotion may be produced by the carcinogen or by other substances (promoting agents), which do not themselves "produce" tumors. Initiation, which is the primary and essential step in the process, is very rapid, but once the initial change has taken place the initiated cells may persist for a considerable time, perhaps the life span of the individual. The most likely site for the primary event is in the genetic material (DNA), although there are other possibilities. The carcinogen is thought to damage or destroy specific genes probably in the stem cell population of the tissue involved.

A compound that reacts with DNA and somehow changes the genetic makeup of the cell is called a mutagen. The mutagens that predispose cells to develop tumors are called initiators and the non-reactive compounds that stimulate tumor development are called promoters. A compound that acts as both an initiator and a promoter is referred to as a 'complete carcinogen' because tumor development can occur without the application of another compound.

Initiation

Initiation is the first step in the two-stage model of cancer development. Initiators, if not already reactive with DNA, are altered (frequently they are made electrophilic) via drug-metabolizing enzymes in the body and are then able to cause changes in DNA (mutations). Since many initiators must be metabolized before becoming active, initiators are often specific to particular tissue types or species. The effects of initiators are irreversible; once a particular cell has been affected by an initiator it is susceptible to promotion until its death. Since initiation is the result of permanent genetic change, any daughter cells produced from the division of the mutated cell will also carry the mutation.

Promotion

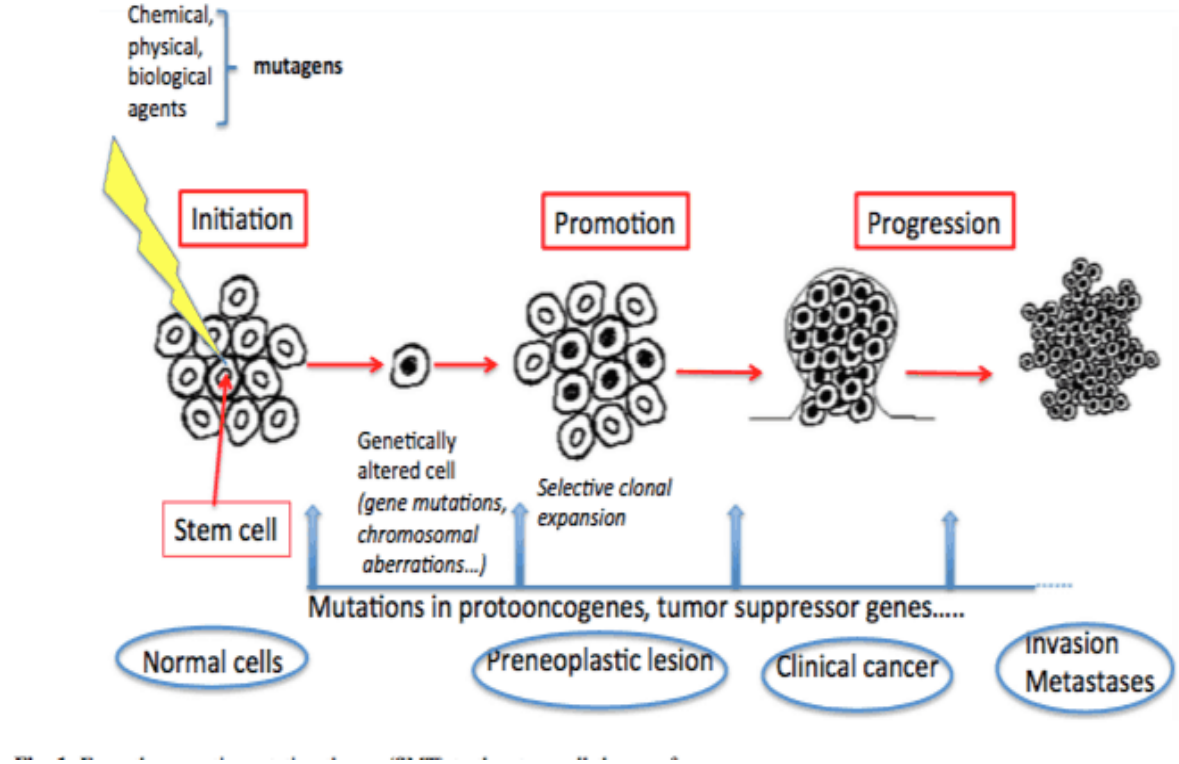
Once a cell has been mutated by an initiator, it is susceptible to the effects of promoters. These compounds promote the proliferation of the cell, giving rise to a large number of daughter cells containing the mutation created by the initiator. Promoters have no effect when the organism in question has not been previously treated with an initiator. Unlike initiators, promoters do not covalently bind to DNA or macromolecules within the cell. Many bind to receptors on the cell surface in order to affect intracellular pathways that lead to increased cell proliferation. There are two general categories of promoters: specific promoters that interact with receptors on or in target cells of defined tissues and nonspecific promoters that alter gene expression without the presence of a known receptor. Promoters are often specific for a particular tissue or species due to their interaction with receptors that are present in different amounts in different tissue types. While the risk of tumor growth with promoter application is dose-dependent, there is both a threshold and a maximum effect of promoters. Very low doses of promoters will not lead to

tumor development and extremely high doses will not produce more risk than moderate levels of exposure.

Progression

In mice, repeated promoter applications on initiator-exposed skin produces benign papillomas. Most of these papillomas regress after treatment is stopped, but some progress to cancer. The frequency of progression suggests that the papillomas that progress to cancer have acquired an additional, spontaneous, mutation. The term progression, coined by Leslie Foulds, refers to the stepwise transformation of a benign tumor to a neoplasm and to malignancy. Progression is associated with a karyotypic change since virtually all tumors that advance are aneuploid (have the wrong number of chromosomes). This karyotypic change is coupled with an increased growth rate, invasiveness, metastasis and an alteration in biochemistry and morphology.

Fig. Factors influencing tumor development showing the progression from normal to invasive tumor.



Metabolic and nutritional alterations in malignancy

1. Abnormalities in metabolism.
2. Anorexia
3. Malabsorption
4. Fluid-electrolyte imbalances
5. Anemia
6. Taste and appetite changes
7. Learned food aversions

8. Hypercalcemia
9. Osteomalcia

1. Abnormalities in metabolism

The extreme weight loss and weakness is caused by abnormalities in glucose metabolism, in which cancer patients cannot produce glucose efficiently from carbohydrates and "feed off" their own tissue protein and convert it to glucose. Glucose intolerance occurs in cancer patients due to increased insulin resistance and due to inadequate insulin release. There is increased lipolysis, free fatty acids, and glycerol turnover and decreased lipogenesis and hyperlipidemia. Fat oxidation rates are higher. The rates of whole body catabolic rate exceeds that of synthetic rate, depletion of body protein occurs. Albumin is depleted in cancer.

2. Anorexia

The anorexia is frequently accompanied by depression or discomfort from normal eating. This contributes further to a limited nutrient intake at the time the disease process causes an increased metabolic rate and nutrient demand. This imbalance of decreased intake and increased demand creates a negative nitrogen balance leading to "cancer cachexia". Loss of appetite can occur due to the systemic effect of the malignant tumor. Anorexia leads to weight loss and malnutrition.

3. Malabsorption:

This can occur due to blind loop syndrome. The associated overgrowth of bacteria in the upper small bowel may result in steatorrhea and vitamin B12 deficiency. Resulting abnormalities of the intestinal epithelium also cause malabsorption. Protein-losing enteropathy can occur in intestinal lymphoma, gastric carcinoma and tumors arising outside the alimentary tract (malignant melonoma). Biliary obstruction due to malignancy can produce deficiency of prothrombin, leading to blood clotting problems and deficiency of bile flow. This in turn interferes with normal digestion and absorption and lead to further decreased calcium absorption and metabolism with subsequent osteomalacia. Protein and electrolyte absorption and other nutrients may also be diminished by solid tumor infiltration of the small intestine or dissemination to lymphnodes. Abdominal tumors may also cause either gastrolic or jejunocolic fistulas. This results in a bypass of the small intestine and contributes to the subsequent malabsorption. Diarrhea and steatorrhea as well as protein loss follow. Extensive protein may also be lost in exudates associated with various gastrointestinal enteropathies.

4. Fluid-electrolyte imbalances:

Gastrointestinal lesions leading to general malabsorption can contribute to fluid and electrolyte losses. Vomiting and diarrhea bring loss of water and loss of water-soluble vitamins. Villous adenoma and adenocarcinomas of the colon can contribute to severe electrolyte imbalance.

5. Anemia:

Anorexia with curtailment of dietary nutrients required for hemoglobin synthesis, iron , protein, folic acid, vitamin B12, and vitamin C as well as malabsorption of these materials can be the underlying cause of anemia. Increase hemolysis, bleeding of ulcerated lesions or presence of gastrointestinal fistulas can also be the contributory factors of anemia.

6. Taste and appetite changes:

These may be due to psychosomatic factors, fear, pain and side effects of medications. Chemotherapy or head and neck radiation may cause taste blindness and inability to distinguish the basic tastes of salt, sweet, sour or bitter with consequent food aversions.

7. Learned food aversions

The fear and uncertainty engendered by the diagnosis of cancer and its uncertain outcome and the stress of diagnostic procedures are exacerbated by the physiologic and metabolic effects of various antitumor interventions. Those stresses can cause learned food aversions. This behavior is the unconscious association of the consumption of a particular food with a concurrent or subsequent unpleasant reaction such as nausea and vomiting. The result is subsequent avoidance of that food.

8. Hypercalcemia:

It is the most common metabolic complications of cancer. Approximately, 20 to 40% of patients with breast, squamous, bladder, and renal carcinoma develop hypercalcemia at some point in their disease.

9. Osteomalcia:

Certain tumors reduce plasma calcitriol concentration in conjunction with hypophosphatemia, thereby inducing an oncogenic osteomalcia. Gastrointestinal malabsorption of calcium and phosphate has been observed.

Types of Cancer Treatment

There are many types of cancer treatment. The types of treatment that one receive will depend on the type of cancer he/she have and how advanced it is. Some people with cancer will have only

one treatment. But most people have a combination of treatments, such as surgery with chemotherapy and/or radiation therapy.

- **SURGERY**

Surgery is a procedure in which a surgeon removes cancer from the body.

- **RADIATION THERAPY**

Radiation therapy is a type of cancer treatment that uses high doses of radiation to kill cancer cells and shrink tumors.

- **CHEMOTHERAPY**

Chemotherapy is a type of cancer treatment that uses drugs to kill cancer cells.

- **IMMUNOTHERAPY TO TREAT CANCER**

Immunotherapy is a type of cancer treatment that helps the immune system fight cancer.

- **TARGETED THERAPY**

Targeted therapy is a type of cancer treatment that targets the changes in cancer cells that help them grow, divide, and spread.

- **HORMONE THERAPY**

Hormone therapy is a treatment that slows or stops the growth of breast and prostate cancers that use hormones to grow.

- **STEM CELL TRANSPLANT**

Stem cell transplants are procedures that restore blood-forming stem cells in cancer patients who have had theirs destroyed by very high doses of chemotherapy or radiation therapy.

- **PRECISION MEDICINE**

Precision medicine helps doctors select treatments that are most likely to help patients based on a genetic understanding of their disease.

NUTRITIONAL PROBLEMS OF CANCER THERAPY

1. Problems related to surgical treatment
2. Problems related to radiotherapy
3. Problems related to chemotherapy

1. Problems related to surgical treatment:

Gastrointestinal surgery poses problems of normal ingestion, digestion and absorption of food nutrients. Head and neck surgery or resections in the oropharyngeal area can greatly affect the food intake. Long term tube feeding may be required in some cases. Gastrectomy may cause numerous post gastrectomy "dumping" problems requiring frequent, small, low carbohydrate feedings. Vagotomy contributes to gastric stasis. Pancreatectomy contributes to loss of digestive enzymes, induced insulin dependent diabetes mellitus and general weight loss.

2. Problems related to radiotherapy:

Radiation to the oropharyngeal area produces a loss of taste sensation with increasing anorexia, nausea and consequent decreased appetite. Abdominal radiation may cause intestinal damage with tissue edema and congestion, decreased peristalsis or endarteritis in small blood vessels. In the intestinal wall there may be fibrosis, stenosis (narrowing), necrosis, or ulceration. If this condition continues over time, it may lead to hemorrhage, obstruction, fistulas, diarrhea or malabsorption. The liver is resistant to damage from radiation in adults, but children are more vulnerable.

3. Problems related to chemotherapy:

These problems are related to-

1. The gastrointestinal symptoms caused by the effect of the toxic drugs on the rapidly developing mucosal cells.
2. The anemia associated with bone marrow effects, and
3. The general systemic toxicity effect on appetite.

The stomatitis, nausea, diarrhea and malabsorption contribute in many food intolerances. Prolonged vomiting affects fluid and electrolyte balance especially in elderly persons. Anti-depressent drugs can cause pressor effects when used with tyramine rich foods.

NUTRITIONAL REQUIREMENTS

Objectives of nutritional therapy:

- To meet the increased metabolic demands of the disease and prevent catabolism as much as possible, and
- To alleviate symptoms resulting from the disease and its treatment through adaptation of food and the feeding process.

1. Energy:

To prevent the excessive weight loss and to meet increased metabolic demands, the total energy value of the diet must be increased. Calorie density sufficient to counter catabolic or hyper-metabolic states and to support necessary anabolism is necessary. Of this total dietary kilocalorie value, there must be sufficient carbohydrate to spare protein for vital tissue synthesis. For an adult patient with good nutritional status about 2000 kcal is recommended. A malnourished patient may require 3000-4000 kcal depending on the degree of malnutrition and body trauma.

2. Protein:

Additional protein is required to provide essential amino acids and nitrogen necessary for tissue regeneration, healing, and rehabilitation. An adult patient with good nutritional status will need about 80 to 100 g to meet maintenance needs and to ensure anabolism. A malnourished patient will need more to replenish tissues and to ensure positive nitrogen balance.

3. Vitamins and minerals:

Optimal intake of vitamins and minerals atleast at recommended dietary allowance levels and frequently augmented with supplements according to nutritional status is indicated.

4. Fluid:

Fluids are increased to compensate losses from gastrointestinal problems as well as any additional loss caused by infections and fever. Sufficient fluid intake is necessary to help the kidneys rid the body of the breakdown products from the destroyed cancer cells and from the drugs themselves. Increased fluid also helps to protect the urinary tract from irritation and inflammation.

Important points to be considered while planning diet for cancer patients:

Oral and other enteral feeding modes are recommended as they pose fewer problems.

- Oral diets can be amplified with nutrient supplements for increased protein, kilocalories, vitamins and minerals.
- Enteral tube feeding with several routes of entry and parenteral nutrition through central and peripheral veins are suggested.
- Based on individual nutritional assessment, a personal food plan is developed with the patient, incorporating desired food forms and family food patterns.
- A number of adjustment in food texture, temperature, amount, timing, taste, appearance and form can be made to help alleviate symptoms.

- Food should be nutrient dense.
- Texture is varied as tolerated, with appeal to sensory perceptions of color, aroma, and taste to enhance the desire to eat.
- A series of mini meals using a wide variety of food items is better tolerated than regular large meals.
- If appetite is better in the morning, a good breakfast should be emphasized.
- Exercise before meals and maintaining surroundings that reduce stress may help in the eating process.
- Zinc supplement may be indicated, as Zn deficiency is related to diminished taste.
- Salivary secretion is also affected by cancer therapy, so foods with a high liquid content should be used.
- Hot, sweet, fatty or spicy foods can enhance nausea, so these foods should be avoided.
- Frequent small meals and snacks, soft in texture, bland in nature and cool to cold in temperature are better tolerated.

Role of food in the prevention of cancer

1. Fruits and Vegetables

Diet rich in fruits and vegetables protects against cancer. The evidence for a protective effect of greater vegetable and fruit consumption is consistent for cancers of the stomach, esophagus, lung, oral cavity, pharynx, endometrium, pancreas, and colon". Allium vegetables (garlic, onion, leeks, and scallions) are particularly potent and have separately been found to be protective for stomach and colorectal cancers and prostate cancer. There are many substances that are protective in fruits and vegetables, so that the entire effect is not very likely to be due to any single nutrient or phytochemical. Possible protective elements are: dithiolthiones, isothiocyanates, indole-32-carbinol, allium compounds, isoflavones, protease inhibitors, saponins, phytosterols, inositol hexaphosphate, vitamin C, D, limonene, lutein, folic acid, beta carotene (and other carotenoids), lycopene, selenium, vitamin E, flavonoids, and dietary fiber.

2. Phytochemicals in the prevention of cancer:

Evidence suggests that dietary phytochemicals/antioxidants can reduce cancer risk. A prospective study showed an inverse association between the intake of flavonoids and the incidence of all sites of cancer combined. Consumption of quercetin in onions and apples was found to be inversely associated with lung cancer risk. The potentially cancer-inducing oxidative damage might be prevented or limited by dietary phytochemicals found in fruit and vegetables. Studies to date have demonstrated that phytochemicals in common fruit and vegetables can have complementary and overlapping mechanisms of action, including modulation of detoxification enzymes, scavenging of oxidative agents, stimulation of the immune system, regulation of gene expression in cell proliferation and apoptosis, hormone metabolism, antibacterial and antiviral effects.

3. Probiotics:

Lactobacillus bulgaricus produced substances which were active against tumor development.

- The anti-carcinogenic properties of lactobacilli fall in to three categories
  1. Inhibition of tumor cells.
  2. Suppression of bacteria which produced enzymes such as β -glucuronidase, nitroreductase and azoreductase, responsible for the release of carcinogens.
  3. Destruction of carcinogens such as nitrosamines.

Intake of fermented or culture containing dairy foods have been reported to reduce the risk of colon cancer. Consumption of products containing viable lactic acid bacteria may lower risk of colon cancer by reducing pro carcinogenic substances or by reducing the level of enzymes (β-glucuronidase, β- glucosidase, azoreductase and nitroreductase) that convert pro carcinogen into carcinogens in the intestine.

4. Vitamin C:

Low blood levels of ascorbic acid are detrimental to health and vitamin C is correlated with overall good health and cancer prevention. At high concentrations ascorbate is preferentially toxic to cancer cells. There is some evidence that large doses of vitamin C, either in multiple divided oral doses or intravenously, have beneficial effects in cancer therapy.

5. Carotene

α -carotene has been found to be a stronger protective agent than its well-known isomer β-carotene. Studies tend to agree that overall intake of carotenoids is more protective than a high intake of a single carotenoid (Stefani, et al. 1999). So, a variety of fruits and vegetables is still a better anti-cancer strategy than just using a single vegetable high in a specific carotenoid.

6. Selenium and Calcium:

Selenium is a mineral with anti-cancer properties. The selenium supplement was most effective in ex-smokers and for those who began the study with the lowest levels of serum selenium. If a person has low selenium levels and other antioxidant defenses are also low the cancer risk is increased even further. High intakes of calcium may reduce the risk for colorectal cancer, perhaps by forming complexes with secondary bile acids in the intestinal lumen or by inhibiting the hyper proliferative effects of dietary haem. Supplemental calcium may have a modest protective effect on the recurrence of colorectal adenomas.

7. Dietary fibers and prebiotics:

The fermentation products of dietary fibers are H_2O, CO_2, CH_4, H_2 and short chain fatty acids (SCFA). Out of various SCFA, butyrate may have the inhibitory effect on colon carcinogenesis. The presence of butyrate in the distal colon is also believed to be important in the prevention of colon cancer, because majority of tumors in both humans and experimentally induced rodent cancer models occur in the distal colon. Water soluble fibers delay starch absorption, stabilizing the serum insulin level that might otherwise increase and promote the intestinal tumerogenesis. Fermentation of dietary fibers result in the formation of SCFA, which lowers the intestinal pH, this in turn inhibit the conversion of primary bile acids to secondary bile acids, also at low pH, the solubility of free bile acids is reduced, diminishing their availability for carcinogenic activity. Prebioticis is a non-digestible food ingredient that beneficially affects the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria in the colon that have the potential to improve host health. Consumption of non-digestible carbohydrates can reduce the concentration of certain biomarkers of carcinogenesis.

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