Dietary Impact in Association to Risk of Cancer and their Anticancer Immune Response

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Abstract

The imbalance between modulation of the cell proliferation and apoptosis results in abnormal cell production which ultimately leads to the cancerous condition. During the 21st century, cancer is probably exceeded to infectious and other chronic diseases as the major cause of death in all countries. The increasing global prevalence ratio and a speedily rising population of cancer survivors focus on the ferocity of public health and economic challenges pretended this disease. This review summarizes the significant outcomes of dietary intake which can enhance the immune response and reduce the risk of cancer. The nutritional general mechanism of action to influence the immune function and the potential activity of anticancer immunotherapy are also studied. For several cancers immunotherapy has developed into standard treatment but considerably remains to be done to prolong the activity of its potential efficiency mainly to cancers that are unaffected within each indication. Although a higher consumption of plant foods like vegetables, fruits, legumes, nuts and whole grains has been suggested for cancer prevention, it has been undecided what is the prime amount of ingestion of these foods and whether particular subtypes are valuable. Several million premature mortalities can be prevented if a high intake of plant foods is adopted globally. Furthermore, for reducing the risk of different types of cancers and slow down their development many dietary products have been proven advantageous.

Keywords: Cancer, Immune system, Dietary items, Immunotherapy, Nutritional balance.

Introduction

Cancer is a major group of diseases observed by the abnormal cells proliferation away from their usual limitations that can then occupy adjoining parts of the body or extent to the other body organs. In 2019, almost 606,880 mortalities were reported in the USA due to the burden of cancer 1. During the 21st century, cancer is probably exceeded the infectious and other chronic diseases as the major cause of death in all the countries 2. Due to the improvements in detection and treatment cancer incidence has fluctuated and survival ratios have enlarged in the USA 1. Therefore, increasing global prevalence ratio and a speedily rising population of cancer survivors focus the ferocity of the public health and economic challenges pretended this disease 2. Public health strategies that are economical and coordinate cancer prevention via behavioral and living modifications are immediately desired 3. One of the adaptable lifestyle factors is a diet that has assembled consideration due to the increasing and significant indications of its capability to stimulus cancer risk. For reducing the risk of chronic diseases like type 2 diabetes, cardiovascular disease and cancer which are the possible risk of premature death globally 4, the populations should adapt to intake a large number of plant products including vegetables, fruits, legumes and whole grains 5. For instance, in 1991 in the United States, a program was launched with the name of 5A Day for Better Health to enhance the consumption of vegetables and fruits to at least 5 servings/d 6. In many other countries, similar movements have also been propelled 7. Different epidemiological studies have shown such recommendations which have significantly exposed that higher consumption of vegetables and fruits reduced the risk of cardiovascular diseases and cancers 7. Furthermore, higher consumption of whole grains and nuts is connected with a reduced risk of type 2 diabetes and coronary artery disease 8, 9. Historically, it was also observed that increased consumption of vegetables and fruits has a greater impact on the reduction of different cancerous conditions. Food, Nutrition and the Prevention of Cancer, the
American Institute of Cancer Research and World Cancer Research Fund when announced their first report published in 1997 explained that there is significant evidence that increased consumption of vegetables and fruits have a significant influence on the reduction of cancers of the breast, mouth, larynx, esophagus, colon, rectum, stomach and bladder 10. However, in the current decades, the evidence for the intake of vegetable and fruit advantages in cancer prevention became less significant as more potential cohort studies complied and exposed deficient or no correlations between vegetables and fruit consumption with the risk of several cancers 11-12. Besides, most accountable cancers for the death rates of women include stomach, cervical, lung and colorectal cancers. For effective anti-cancer therapy, only 30% of underprivileged countries are capable to provide associated facilities. Due to cancer treatment, the annual burden on the world economy is about US$ 1.16 trillion. To reduce such an economic burden and increase the quality of life non-pharmacological methods such as steady physical activity and healthy nutritional habits should be encouraged which ultimately promoted conventional anti-cancer therapies. This review summarizes the significant outcomes of dietary intake which can enhance the immune response and reduce the risk of cancer. The nutritional general mechanism of action to influence the immune function and the potential activity of anticancer immunotherapy are also studied.

**Immunotherapy: Current status**

By presenting immunotherapy as a standard first and second-line modality checkpoint inhibitor therapy has carried a paradigm modification in the treatment of progressive cancer. The treatment with immunotherapy agents has a major benefit in the long-term significant potency as compared to other regular therapies like pathway inhibitors or chemotherapy. Though, only a subgroup of cancers inside each signals feedback to this therapy leaving the majority of patients unaffected by this potentially curative modality 13. Recently, it was observed according to a degenerate method based on genetic instability that human cancers progress ensuing a severe selection bottleneck and degenerative method connected with increased metabolic activity of glucose associated with an increase in the level of lactate and the adenosine pathway, the decrease of tryptophan and arginine level, all have a significant impact on the immune mechanism inside the TME. It is also observed that the general metabolic methods influential deviation from ideal body weight extremely impacts the immune status. Moreover, important dietary components like vitamins may be regulated by the nutritional status and secondarily affect immune function 17-18.

**Correlation between immunity and nutrition**

Food signifies not only a potential component of body maintenance and growth but also involves some compounds which act as antigens. Particularly, throughout the lamina propria an innate and adaptive immune cell distributed or involves the secondary lymphoid organs like colonic lymphoid follicles and Peyer’s patches can provoke robust feedback when triggered by food antigens. It has been observed that food intake leads to a situation of post-prandial mild inflammation, which are not only local but also systemic 19. In healthy volunteers after a 1-hour intake of a western-type hyper caloric breakfast serum levels of the inflammatory interleukin (IL)-17, cytokine, intensely increase 20. Among the control group individuals, this phenomenon was not observed who ingested breakfast along with polyphenols containing fruit juice. These components are recognized by a significant anti-inflammatory potential, which leads to the reduction of IL-17 serum values. Among the normal-weight children an experiment was conducted, they recommended a one-year Mediterranean diet (MD) compared to age complemented controls, who omitted health food endorsements, revealed variable immune profiles 21. The outcomes of the experiment showed that the levels of IL-17 decreased while, salivary levels of the anti-inflammatory cytokine, IL-10 increased. In another group of children who mostly intake “junk food” a considerable increase in IL-17 was detected. According to this, IL-10 is a cytokine primarily produced by FOXP3+ T regulatory (TREG) cells, which are convinced in the intestine by some dietary components, such as vitamins (A and D), polyunsaturated fatty acids (omega-3) and polyphenols. Immunosenescence is recognized as the failure of the immune mechanism with age which leads to the increased incidence of infections, autoimmune and neoplastic diseases in aging 22. During the aging hypo-nutrition intensifies the previously impaired immunity, subsequently, aged people are commonly malnourished concerning unfortunate socio-economic conditions, mental illnesses and tooth loss 23. Most significantly, in the elderly lack of proteins and oligo-elements regulates severe immune insufficiency, which can be serious. For example, among the elder’s zinc deficiency is very common but undiagnosed, which leading to increased incidence of respiratory infections, T cell malfunction and reduced feedback to vaccination 24. Thus, among the elders with zinc deficiency, zinc supplementation is very effective for the treatment of chronic diseases 25. Different studies suggested among the natural products the usage of red grape polyphenols to elder individuals restores weakened T cell functions and much effective during winter infections 26. Furthermore, to restore innate and adaptive immunity among aged people the administration of probiotics and symbiotics is very effective, also enhancing the activity of intestinal microbiota which under normal situation plays their role in immune homeostasis along with balancing the symmetry between TREG cells and Th17 cells 27. From circulation origins cancerous cells such as monocytes plays a significant role in the tumour microenvironment 28. Monocytes segregate into tumour-associated macrophages.
(TAMs), whose concentration completely associates with tumour progression. T cytokotoxic (Tc) cells are also present in extremely immunogenic tumours, which account for the tumour demolition or at least restrain the cancer growth. Therefore, TAMs and tumour cells produce suppressive cytokines which ultimately diminish T cell-mediated cytotoxicity. Cancer cells as well as TAMs produce a group of pro-inflammatory cytokines like IL-6, TNF-alpha and IL-1 beta with the activation of transcription factors STAT3 and NF-kB. Besides, TAMs employ carcinogenic effects, which producing growth factors or releasing cytokines, such as IL-6, which demonstrate anti-apoptotic activities on cancer cells. It should be highlighted, however, the immune intrudes within the tumour microenvironment are considered by natural plasticity and their functional coordination can be regressed by dissimilarity in the intra-tumour homeostasis prompted by several exogenous agents such as immunotherapy or environmentally associated factors such as co-morbidities, diet and microbiota.

**Dietary products that increase the risk of cancer**

Several studies have explored the link between diet and certain cancers including breast, prostate and colorectal cancer. Some epidemiological evidence has shown that those who consume very fewer fruits and vegetables have a high risk of cancer in comparison with those who consume a good amount of the same. 128 out of 156 dietary studies reported statistically eloquent protective effects of consuming fruits and vegetables against cancer. It indicates the inverse relationship between intake of fruits and vegetables with the risk of several cancers. Scientific investigations have found that exposure to many additives (nitrates and nitrates); food contaminants and dietary components have the carcinogenic potential. People are failing to extract time for their health wellness. Even they do not hesitate to compromise their health while buying and eating packaged, processed, or artificially colored food. A study has revealed the occurrence of 80% of colorectal cancer due to dietary reasons.

**Drinking water polluted with heavy metals**

In some Indian state’s cities situated close to the Ganga River and its subsidiaries, high levels of heavy metals have been noted. Heavy metals (mercury, arsenic, lead, cadmium, chromium) induce the generation of reactive oxygen species which can cause DNA lesions and subsequently promote carcinogenesis. Histopathology reports and spectrophotometric assessment of gall bladder cancer patients living in those areas confirmed elevated levels of heavy metals like arsenic, mercury, lead, cadmium, and chromium in affected tissues and bile. These findings indicate the link of heavy metal with gall bladder cancer.

**Processed foods**

A significant association was observed between the higher intake of pickled vegetables salted meat and the higher risk of gastric cancer in the Chinese population. Reduced intake of salt processed foods may reduce the chances of getting gastric, colon, rectum, pancreas, lung, bladder cancer. High-temperature processing, barbecuing of meat initiates a reaction between amino acids and sugars (Maillard reaction) that results in the production of heterocyclic amines (HACs) like 8-dimethyl imidazole quinoxaline (MeIQx) and the 2-Amino-1-methyl6 phenylimidazo pyridine (PhIP) which are classified as potentially carcinogenic compound for human. Incomplete combustion of oil or cooking food by smoking produces polycyclic aromatic hydrocarbons (PAHs) like benzopyrene which is a potential carcinogen. DNA mutation is the suggested reason for carcinogenesis caused by PHAs and HACs.

**Food dyes**

People are more affectionate for colorful food allocations but they are not aware of possible risks. But food dyes like Blue1, Blue2, Citrus Red2, Green3, Orange B, Red3 and Yellow6 have been found to cause kidney, thyroid, brain, adrenal, bladder and testicular tumors in rodent studies. Clinical studies are needed to investigate the effects on humans.

**Fast foods**

Fried fast foods, sweetened drinks and the other foods with a high glycemic index are noted to increase the risk of colorectal cancer. It has been investigated that high fat-containing fast food consumption ultimately causes the possible increase of polycyclic aromatic hydrocarbons (PAHs) and such fats potentially affected the gastrointestinal tract of the body. These findings point towards increasing the serious risk of the development of cancer with a frequency of fast-food intake.

**Aflatoxins**

These are toxic metabolites of certain fungi. *Aspergillus flavus* is one of the famous sources of aflatoxin that can infect many nuts and grains. Milk produced by mammals eating this infected foodstuff can pass aflatoxins to their infants. The Department of food safety and zoonoses of the World Health Organization in 2018 published a report that people who get exposed to aflatoxin B1 for the long term become more vulnerable to get suffered from liver and kidney cancer.

**Acetaldehyde**

Humans may get acetaldehyde exposure from various foods, metabolism of ethanol. Binding to DNA acetaldehyde forms stable DNA adducts and also interferes with DNA repair processes which may promote carcinogenesis. With sound evidence, heavy drinkers are known to be highly vulnerable to mucosal hyperproliferation of the upper aerodigestive tract, large intestine and cancers of the upper respiratory tract.

**Dietary products that reduce the risk of cancer**

**Foods containing Omega-3 fatty acids**

Nowadays, several cancer researchers have started exploring apoptosis (natural cell death) as a target for anticancer therapy and they have noted overexpression of antiapoptotic proteins and under-expression of proapoptotic proteins in cancer cases. Reports also claim that disturbed apoptosis circuitry is highly associated with oncogenicity. PUFA s such as omega-3 fatty acids including Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) can reduce the proliferation of cancer cells and induce apoptosis both in vivo and in vitro. Furthermore, these polyunsaturated fatty acids are found valuable for cancer prevention and improving the efficacy of certain antineoplastic drugs.

**Capsaicin**

Pungent phytochemical capsaicin present in peppers (widely used spices) is well known for having anti-oxidant and anti-inflammatory potential. Capsaicin has been explored and proved to have anticancer properties by altering the expression of some genes involved in angiogenesis, cancer cell survival and growth arrest. Capsaicin strengthens the fight against human glioma, myeloma, osteosarcoma and colorectal cancers by accelerating apoptosis rate.
**Cruciferous vegetables**

These vegetables such as Brussels sprouts, Bok choy, Cauliflower, Cabbage, Broccoli, belong to the family Cruciferae or Brassicaceae. Cruciferous vegetables are major sources of sulfur-associated compounds like glucosinolates and hydrolysis of these compounds during chopping and chewing of cruciferous vegetables result in products like indole-3-carbinol (I3C) and isothiocyanates.

**Olive oil**

It is a blend of oleic acid, linoleic acid, secoiridoids, squalene, tyrosol, hydroxytyrosol (HT), lignans, flavonoids, triterpenes, and high abundance of polyphenols is evident in extra virgin olive oil. Extra virgin olive oil is obtained from olives by pressing them without heat and chemical treatment. In the Mediterranean region olives are freely consumed and olive oil is the cooking fat of choice; and epidemiological studies relate this liberal consumption of olive oil with significantly fewer incidences of colorectal, breast and skin cancer in this region. Furthermore, squalene (abundantly found in Olive oil) is known for the tumor-inhibiting property.

### Table 1: Different compounds present in cruciferous vegetables to reduce the risk of cancer

| Compounds                      | Mechanism                                                                 | Cell lines                                         | Ref. |
|--------------------------------|---------------------------------------------------------------------------|----------------------------------------------------|------|
| Indole-3 carbinol (I3C)        | G1 cell cycle termination PC-3 cells due to variations occurred in G1 cell cycle proteins | Human prostate cancer cell line PC-3              | 71   |
| Indole-3 carbinol (I3C)        | Inhibits protein kinase B/Akt and Influence apoptosis                     | Human breast tumor cell line MDA MB468             | 72   |
| Indole-3 carbinol (I3C)        | Reactivation of a potent tumor suppressor gene PTEN                       | Human cell lines, Wwp1-/- mice and its paired Wwp1+/+ mice | 66   |
| 3,3'-diindolylmethane (DIM)    | Rises of p21 protein and mRNA levels and induce G1 cell-cycle arrest      | Human breast adenocarcinoma cell lines MCF-7 (estrogen dependent) and MDA MB-231 (estrogen independent) | 73   |

### Table 2: Capsaicin cancer preventing mechanism of actions

| Mechanism of actions                        | Cell lines                                         | Ref. |
|---------------------------------------------|----------------------------------------------------|------|
| Stimulation of Fas/CD95 mediated apoptosis  | Human urothelial cancer cells                      | 74   |
| Induces TRPV6 receptor and calpain pathway mediated apoptosis | Human small cell lung cancer cell lines (NCI-H82, NCI-H69, DMSS 3, DMS114) | 75   |
| Stimulation of TRPV1 vanilloid receptor-mediated apoptosis | Human glioma cells                                | 76   |
| Cell cycle arrest at G2/M phase             | Human KB cancer cells                              | 77   |
| Degeneracy of mitochondrial membrane potential |                                                   |      |

### Table 3: Olive oil compounds anti-cancer mechanism of action

| Olive compounds | Biological effects          | Cell lines                                         | Ref. |
|-----------------|-----------------------------|----------------------------------------------------|------|
| Hydroxytyrosol  | Apoptosis induction         | Estrogen receptor negative SKBR3 breast cancer cell | 78   |
| Oleuropein      | Reduced angiogenesis        | Human umbilical vein endothelial cells             | 78   |
| Oleocanthal     | Inhibition of acid sphingomyelinase | Human pancreas adenocarcinoma, BxPC3 cells   | 79   |
| Oleocanthal     | Cytotoxicity induction of apoptosis | Human breast cancer MDA-MB-231, MCF-7, and T-47D cells   | 80   |
| Oleuropein      | Cell cycle delay at S phase | MDA-MB-231 and MCF-7 human breast cancer cell lines | 81   |
Garlic and Onions
A large number of epidemiological studies have provided strong evidence in favor of cancer (especially gastrointestinal and esophageal) preventing effects of Allium genus vegetables including garlic and onions. Heating badly influences the anticancer property of garlic as it has been noted that microwaving for 60 seconds or 45 minutes oven heating of uncrushed garlic leads to a significant weakening of the anticancer effect exhibited by garlic. A 2016 study on Chinese lung cancer patients suggested the significant inverse association of raw garlic intake with the development of lung cancer in a dose-dependent manner when compared to no intake. It has been proved that garlic extract augments the anticancer effect of existing antineoplastic drugs such as cisplatin, docetaxel and gemcitabine.

Lycopene foods
Lycopene (a red carotenoid) is abundantly found in ripe tomatoes, red watermelon and grapefruits. It prevents oxidative damage of DNA by fighting against free radicals and in this way, it slows the transformation of normal cells to cancerous cells. Voluminous evidence about its anti-oxidant, anti-proliferative, pro-apoptotic activities against oral and prostate cancer are available.

Table 4: Lycopene cancer preventing mechanism of actions

| Mechanism of actions                                      | Cell lines                                      | Ref. |
|-----------------------------------------------------------|-------------------------------------------------|------|
| Cell cycle arrest, rise in apoptosis, inhibition of cell growth | Human prostate, breast, colon, liver, larynx, and cervical cancer lines | 82   |
| Cell growth arrest and apoptosis                           | Androgen-independent DU145, PC-3, and androgen-dependent LNCaP human prostate cancer cells | 83   |
| G0-G1 cell cycle arrest, apoptosis via significant suppression of ERK (extracellular signal-regulated kinase) signalling pathway | Human gastric HGC-27 cell line | 84   |

Conclusion
The outcomes of the current study concluded that the increased intake of different processed food, drinking water containing heavy metals; food colors and infected nuts are the possible risk factors of several cancers. Cancer patient's histopathological analysis exposed the correlation of dietary intake and cancer risk. Higher intake of plant foods such as vegetables, fruits, legumes, nuts and whole grains are of greater importance for reducing the risk of various cancers and premature deaths. The current outcome strongly recommends a higher intake of fruits and vegetables. While the possible mechanism that may influence the immune system and thus cancer growth and feedback to immunotherapy agents have been exposed, insufficient information is available about how they may influence and regulate the therapies since limitations relating dietary habits to clinical consequence during immunotherapy are not regularly included. Comprehensive information about the diet and nutritional status should be measured in association with immunotherapy trials. A massive campaign should be launched to aware the community of the importance of diet and routine lifestyle for increasing immunity against cancer. For the dietary anticancer and carcinogenic potential extensive quantitative examination should be performed on a large scale.

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