Review Article

Understanding cancer etiology: A review of the evidence-based Ayurvedic framework of cancer etiologies

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Abstract

Background of the Study: As many as 10 million people have died from cancer globally in 2020, making it the top cause of mortality in the globe. Cancer develops as a result of the multi-stage process by which normal cells convert into tumor cells, progressing from a precancerous lesion to a malignant tumor. By avoiding risk factors and applying existing evidence-based preventative techniques, 30%–50% of malignancies may be averted. In order to avoid cancer, it is essential to know the specific causes of the disease. *Nidanas*, or etiologies, are well-described in Ayurvedic science. Here, the causes of cancer have been outlined so that the knowledge may be used effectively to avoid the disease. **Aims:** Identification of cancer etiologies that have been described in classics. Evidence-based understanding of these etiologies and to comprehend the significance of etiologies in cancer prevention. **Materials and methods:** A thorough evaluation of literature, including ancient Ayurvedic classics, modern medical texts, and articles published in reputable journals, was conducted to meet the study's goals and objectives. **Results:** According to Ayurveda, there are three distinct phases of tumorigenesis: chronic inflammation, precancerous development, *Granthi* (a benign glandular swelli ng), and *Arbuda* (a precancerous tumor) (definite malignancy). A growing body of evidence suggests that the tumor microenvironment, which is predominantly controlled by inflammatory cells, is an essential player in the neoplastic process. **Conclusion:** Although inflammation is coming into the picture just now in the contemporary world, Ayurveda has described this as a leading cause 5000 years back. It is evident that diet and lifestyle play a crucial role in the etiology of *Shoth* (inflammation).

Keywords: *Arbuda*, Ayurvedic neoplasms, *Granthi, Nidanaparivarjana, Shotha*

Introduction

Cancer is a generic term for a large group of diseases that can affect any body part. Other terms used are malignant tumors and neoplasms. One defining feature of cancer is the rapid creation of abnormal cells that grow beyond their usual boundaries, which can then invade adjoining parts of the body and spread to other organs; the latter process is referred to as metastasis. Widespread metastases are the primary cause of death from cancer.[1]

Cancer is a major burden of disease worldwide.[2] It is estimated that in India, the total cancer cases are likely to go up from 979,786 cases in the year 2010 to 1,148,757 cases in the year 2020.[3] It is estimated that there were 19.3 million new cancer cases and 10.0 million cancer deaths in 2020 worldwide.[1] There is about a 20% risk of getting cancer in a lifetime (before the age of 75), and a 10% risk of dying from the cancer; one in five persons will get cancer in their lifetimes and one in 10 will die from the disease. With 2.26 million new cases estimated in 2020, female breast cancer has now become the most commonly diagnosed cancer worldwide, followed closely by lung cancer (2.21 million).[1] The most common cause of cancer death remains by far lung cancer (1.80 million deaths), followed by liver (0.83 million) and stomach cancer (0.77 million).[1]

The growing incidence of cancer indicates an urgent need for strengthening and augmenting the existing diagnostic and treatment facilities, which are inadequate even to confront the present load.[4] It is also evident that therapeutic interventions

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had less success in reducing deaths from most cancers.[5] Given the continued growth in the number of persons with cancer, the primary prevention of cancer remains an urgent public health priority. This study summarizes risk factors or etiologies of cancer based on *Ayurvedic* framework, to understand them and come up with possible strategies to prevent cancer.

Cancer is a multi-factorial disease, and treating it as such requires a multifaceted strategy. Ayurveda, the science of life, has long emphasized the need of taking a comprehensive approach to preserving good health and preventing illness. Scientists and academics are now looking for ways to use Ayurveda to prevent and treat cancer.

Ayurvedic concept of cancer

Ayurveda, an Indian system of treatment that has been around for over 5000 years and is still effective, may not be acquainted with the word "cancer" Ayurveda classics are fully aware of clinical characteristics comparable to cancer. Ayurveda classics describe cancer as *Granthi* (benign tumor) and *Arbuda* (malignant tumor) and elaborate *Shotha* (inflammation) as the primary cause for the same.[6]

One or two of the three-body systems (*Vata, Pitta,* and *Kapha*) are out of balance in the benign neoplasm and are not too damaged as the body still tries to coordinate between the three systems. Malignant tumors are highly dangerous since all three of the main body systems lose reciprocal coordination and cannot thus avoid damage to the tissue, which leads to fatal morbidity. These are very harmful as the body fails to maintain normalcy and loses coordination.

Pathogenesis of cancer in Ayurveda framework: Inflammation and cancer

Ayurveda describes different stages of tumorigenesis as chronic inflammatory and intractable diseases. Research strongly suggests that chronic inflammation is associated with serious lifestyle and age-related diseases such as cancer and metabolic syndrome. Evidence also suggests that inflammatory microenvironment in and around tumors is an essential part of tumorigenesis. The molecular nature of the causal relationship between inflammation and cancer is only now being understood.[7] [Figure 1]

Once an inflammatory microenvironment has been created in tumors, there are mechanisms that sustain it. One mechanism involves inflammation induced by reactive oxygen and nitrogen species. These free radicals damage DNA, proteins, and lipids and result in gene mutation and accumulation of advanced glycation end products (AGE). Interaction of AGE with its receptor AGE triggers chronic inflammation by activation of NF-κB, at sites of tissue damage.[8]

Aims and objectives

a. Identification of etiologies described in classics for cancer
b. To understand the importance of studying etiologies in the p revention of cancer with evidence-based approach.

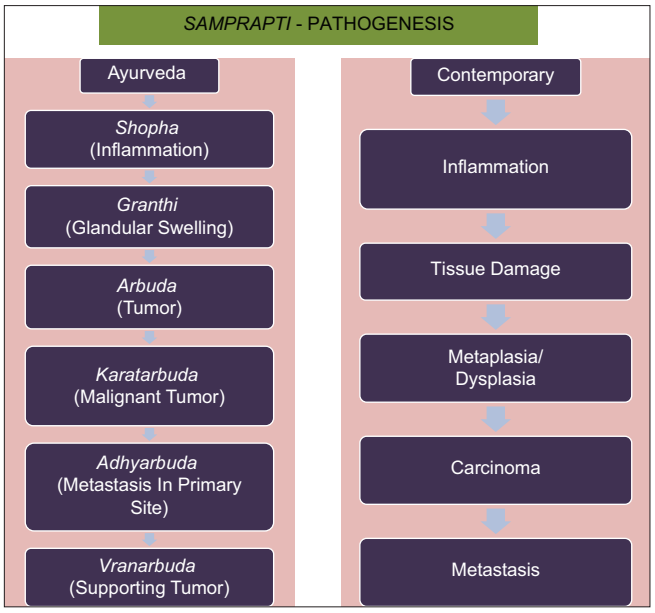

Figure 1: Explaining *Samprapti* of cancer

Materials and methods

A thorough evaluation of literature, including ancient Ayurvedic books, modern medical texts, and articles published in reputable journals, was conducted to meet the study's goals and objectives. Evidence was gathered from a variety of observatory and cohort studies published in reputable journals to support the theoretical concept.

Results

Etiologies/risk factors for cancer

It is difficult to pinpoint why one individual develops cancer while another does not. Certain risk factors, however, have been demonstrated in studies to enhance a person's odds of acquiring cancer. These risk factors play a great role in Ayurveda and it is the primary step to ward off the diseases even before they have occurred.[9] Risk factors can be modifiable[10] or nonmodifiable.[11]

Certain *Nidanas* which contribute to the formation of *Granthi* and *Arbuda* have been described in detail by Acharya Charaka, which is compiled in Table 1, and discussed in detail.

Discussion

According to Acharya Charaka, certain diseases, when not treated properly, end up creating complications like *Shotha* (inflammation), which is, of course, the very first step in the etiopathogenesis of cancer.[12] Some of the diseases that Charaka mentioned have listed below with possible evidence:

Kasa (cough) *Shwasa* (breathlessness/shortness of breath)

These are the crucial symptoms of many respiratory disorders such as chronic obstructive pulmonary disease (COPD),

Table 1: Illustrates the *Nidana* (etiology) of cancer and their possible contemporary correlation

***Nidana* (c.su. 18/6)**	**Possible correlation**
Ahara	
Guru, Pishtanna, *Snigdha Dravya*	High-calorie, high-fat, trans-fatty acids
Amla, Lavana	Vinegar, salty, spicy
Nootan Shuka Dhaanya and *Shami Dhaanya*	Food articles with high GI
Aanupa and *Udaka Mamsa*	Red meat has a high intake of seafood
Dadhi-Manthaka Virudha	Curd, yogurt, sprouts
Nidra	
Ratri jagarana	Shift workers
Brahmacharya (lifestyle)	
Avyayama	Physical inactivity
As a complication of diseases	
Kasa, Shwasa	Present as a symptom in COPD, pulmonary fibrosis, and pulmonary tuberculosis
Udara Roga	NAFLD, cirrhosis
Pradara	Present as a symptom in HPV and BV
Bhagandar, Arsha	Fistula, hemorrhoids
Kushta	Psoriasis
Pandu	Anemia

BV: Bacterial vaginosis, HPV: Human papillomavirus, NAFLD: Nonalcoholic fatty liver disease, COPD: Chronic obstructive pulmonary disease, GI: Glycemic index

(emphysema, chronic bronchitis) pulmonary fibrosis, and pulmonary tuberculosis (TB).

Pulmonary tuberculosis and lung cancer

Lung cancer and TB are major causes of illness and death across the globe. TB may raise the risk of lung cancer by causing significant and long-term pulmonary inflammation. However, there are little prospective data on TB and lung cancer risk.[13]

Based on data from the Taiwan National Health Insurance Database, a countrywide population-based cohort research was undertaken. Between 1997 and 2008, 5657 TB patients and 23,984 age- and gender-matched controls were recruited for the research. The incidence rate of lung cancer (269/100,000 person-years) was substantially greater in pulmonary TB patients than in controls, and pulmonary TB infection is linked to a higher risk of lung cancer.[14]

In a subsequent cohort study of 716,872 cancer-free insured people aged 20 and above, 4480 individuals with newly diagnosed TB were identified from universal insurance claims in 1998–2000 and followed until 2007. The incidence of lung cancer in the two cohorts was compared, and the risk of acquiring lung cancer was calculated. Lung cancer was shown to be 11 times higher in TB patients than in non TB individuals. The TB cohort had a hazard ratio of 4.37, according to Cox proportional hazard regression analysis. With the combined impact of COPD, the hazard ratio climbed to 6.22, or to 15.5, with the combined effect of other smoking-related malignancies.[15]

Chronic obstructive pulmonary disease and lung cancer

COPD patients have a higher risk of lung cancer,[16] suggesting that common pathogenic mechanisms such as chronic inflammation, epigenetic alterations, and poor DNA repair pathways as a consequence of oxidative stress are involved.[17] Exogenous and endogenous oxidative stress, autoantibody expression, protease activity, and the production of pro-inflammatory cytokines are all known to damage the lungs in persons with COPD by causing airway destruction, lung hyperinflation, and air trapping.[18-20]

In smokers with surgically resectable NSCLC, a research was conducted to see whether COPD is a risk factor for the squamous cell carcinoma (SCC) histological subtype. There were 86 cases and 54 controls (mostly adenocarcinoma). The study concluded that COPD increased the risk of SCC by four times.[21]

Pulmonary fibrosis

Idiopathic pulmonary fibrosis (IPF) was reported to be associated with an increased risk of lung cancer as a result of the occurrence of atypical or dysplastic epithelial changes in fibrosis, which progressed to invasive malignancy.

A study was conducted to establish the link which established. Overall, the incidence of cancer increased in people with IPF compared to the general population.[22]

Kustha (psoriasis) and skin cancer

Patients with psoriasis have an increased risk of cancer, which may be due to impaired immune surveillance, immune modulatory treatments, chronic inflammation, and/or co-risk factors such as obesity.[23-29]

A cohort study was conducted to establish the link of psoriasis and increased cancer risk, which suggested that there is a small increased risk of cancer overall in patients with psoriasis. Patients with psoriasis who received treatment with systemic medications or phototherapy were shown to be at a higher risk for malignant neoplasms compared with controls.[30] Another meta-analysis demonstrated that compared with patients without psoriasis, patients with psoriasis had a 1.72 times higher risk of developing nonmelanoma skin cancer.[30]

Pandu (anemia) and cancer

There are several types of anemia; however, iron-deficiency anemia is most often linked to cancer. Iron-deficiency anemia is caused by a lack of healthy red blood cells in the body.[31,32]

A large cohort of oncology patients was studied to determine the incidence of cancer-related anemia, and if inflammation and malnutrition predicted its severity. Between May 2011 and January 2014, 888 cancer patients were studied at several venues. Before any cancer therapy, patients were evaluated. Anemia prevalence was examined by clinical variables (tumor location, stage, and performance status). The modified Glasgow prognostic score (GPS), a composite measure of malnutrition

and inflammation, was analyzed in each patient and its relevance in predicting hemoglobin level. Anemia affected 63% of patients, with the lowest hemoglobin levels reported in individuals with advanced cancer and reduced function. Ovarian cancer patients had the lowest hemoglobin levels. Hepcidin, ferritin, erythropoietin, and reactive oxygen species were negatively connected with hemoglobin, whereas leptin, albumin, cholesterol, and antioxidant enzymes were favorably correlated. Hemoglobin concentration was predicted by stage, interleukin-6, and leptin. Hemoglobin also correlated with a modified GPS. Finally, immunological, dietary, and metabolic factors influence the severity of cancer-related anemia. To offer safe and effective customized therapy, doctors must first understand the pathophysiology of cancer-related anemia.[33]

Pradara (vaginal discharge) and cancer

Vaginal discharges are a sign of underlying infections in the vaginal area. Although symptoms can be effectively treated with chemotherapy, the presence of the symptom for an extended period, combined with unsanitary settings, may aggravate the situation.[34]

Human papillomavirus

The primary cause of precancerous and cancerous cervical lesions is infection with high-risk or oncogenic human papillomavirus (HPV) types. Most cases of cervical cancer occur as a result of infection with HPV16 and 18. High-risk types, especially HPV16, are found to be highly prevalent in human populations.[35,36]

Bacterial vaginosis

A systematic review and meta-analysis study was conducted to summarize published literature on the association between bacterial vaginosis (BV) and cervical precancerous lesions. Out of 329 articles, 17 cross-sectional and two incidence studies were selected and the study established the link between BV and Cervical Cancer.[37]

Udara Roga (diseases related to the abdomen)

Nonalcoholic fatty liver disease

In many countries, nonalcoholic fatty liver disease (NAFLD) is expected to overtake alcohol as the major cause of hepatocellular carcinoma (HCC). Obesity, diabetes, Hispanic ethnicity, and genetic variants in PNPLA3, TM6SF2, GCKR, MBOAT7, and HSD17B13 are among the risk factors for NAFLD that are also linked to HCC. Hepatocarcinogenesis can be triggered by steatosis-related lipotoxicity and oxidative DNA damage. These factors could account for the link between NAFLD and HCC, particularly in the absence of cirrhosis.[38]

Cirrhosis

In a Danish cohort study, the clearest finding was an increased risk of liver cancer in all cirrhosis patients, regardless of the type of cirrhosis. Cirrhosis appears to be a necessary step in the development of liver cancer. Cirrhosis-related hormonal and immunological alterations had no discernible impact on the incidence of hormone malignancies or cancers linked to immunosuppression. It's possible that the increased risk of breast cancer in alcoholic cirrhosis is due to a direct action of alcohol rather than an increase in estrogen levels. Many additional malignancies are increased in cirrhosis patients; however, several are highly influenced by alcohol and tobacco use.[39,40]

Arsha and Bhagandar (hemorrhoids and fistula)

Hemorrhoids

A cohort retrospective study demonstrated that patients with hemorrhoids were at a nearly twofold increased risk of developing colorectal cancer (CRC). Hemorrhoidectomy is seen as a benefit to hemorrhoid patients since it provides a near 50% risk reduction of subsequent CRC.[41]

Fistula

In Crohn's disease (CD) patients, cancer arising at the site of a chronic perianal fistula is uncommon. Chronic inflammation of the ano-rectal mucosa, delayed wound healing, and cell turnover may all play a role in the development of perianal fistula in CD and SCC. Patients with colonic CD who also have rectal involvement are more likely to develop perianal fistulas (92%). Carcinoma is found in 0.7% of patients with perianal CD.[42,43]

Ahara (diet)

High-fat diet/high-calorie diet/trans-fatty acids

Gastrointestinal cancer is arguably one of the best causes of cancer death. Inflammation and metabolic alterations connected to a high-fat diet have been linked to various digestive system illnesses and cancers.[44]

Animal studies relate HFD consumption to an increased risk of colon cancer. A Western-style diet increased the number of polyps in the Apcmin/+ mouse model of intestinal carcinogenesis by 75% (40% calories from fat). Obesity (60% fat) has also been reported to promote Azoxymethane-induced abnormal crypt foci in the colon. In addition, obese animals with an HFD (60% fat) had increased proliferation and decreased apoptosis in the colonic epithelium.[45]

Salt and highly acidic food: Risk of cancer

Stomach cancer is the fourth-most prevalent and third-most lethal cancer.[46,47] Infection with *helicobacter pylori* (*H. pylori*), salt-preserved foods, dietary nitrite, smoking, alcohol, obesity, radiation, and family history have all been linked to stomach cancer.[48,49] Oncologists have explored the potential synergistic association between salt consumption and *H. pylori* infection in the development of stomach cancer in three prior epidemiological investigations. High intakes of salt, pickled food, and processed meat are associated with significantly increased risks of gastric cancer; these increased risks are also seen when participants consume moderate amounts of salt.

One hundred and thirty newly diagnosed bladder cancer patients and the same number of individually matched controls were included in a hospital-based case–control study. Liver, canned meat, pork, and vinegar intake were found to be risk factors for bladder cancer, whereas frequent daily urination,

fruit juice drinking, and cabbage consumption were found to be protective factors.[50]

Alcohol

Alcohol consumption has been linked to an increased risk of oral, pharyngeal, laryngeal, esophageal, liver, large intestine, and female breast cancer. The relationship between alcohol use and stomach, pancreatic, lung, bladder, prostate, endometrial, ovary, cervix, and skin cancers is disputed. Few studies have shown an inverse (i.e., protective) relationship between alcohol use and the risk of renal cell carcinoma and hematologic malignancies. A complete investigation of the impact of alcohol on cancer risk should look at all cancers and their subtypes. Although heavy drinking is associated with an increased risk of cancer, some studies link light to moderate drinking to an increased risk of cancer.

A cohort study of 124,193 persons was conducted where subjects were, from 1978 to 1985 and followed until December 31, 2012 or until a diagnosis of cancer, their death. The study concluded that heavy drinking (≥3 drinks per day) was associated with an increased risk of 5 cancer types: upper airway/digestive tract, lung, female breast, colorectal, and melanoma, with light-to-moderate drinking related to all but lung cancer.[51]

Glycemic index

Glucose metabolism-related factors appear to be associated with numerous malignancies. Most carbs raise blood glucose and insulin levels. However, the magnitude varies depending on carbohydrate type, digestion, consumption, and other nutrients. The glycemic index (GI) assesses carbohydrate items based on their tendency to raise blood glucose levels. High GI meals, such white bread, produce a quick rise in blood glucose. Low-GI meals like lentils and pasta digest more slowly, causing a slower blood glucose rise. The glycemic load (GL) was established to reflect the effect of total carbohydrate consumption: it is a measure of total glycemic effect and hence an indicator of the diet's insulin demands.

Several observational studies have examined dietary GI/GL and cancer risk, with inconsistent results. Three meta-analyses established a link between high GI and CRC in both case–control and cohort studies. Meta-analyses linked high GI and GL to a higher risk of breast cancer and diabetes-related malignancies but not endometrial cancer. Other malignancies appear to be unaffected by dietary GI or GL6.[52]

Red meat and high consumption of seafood

Most diets rely on meat for protein and fat. Consumption of meat, particularly red meat, is linked to an increased risk of diabetes, cardiovascular disease, and some malignancies.

Several prospective studies were published in the late twentieth century. The US Nurses' Health Study found a substantial link between beef, pork, and lamb consumption and colon cancer. There were 150 colon cancer cases among 88,751 women followed for 6 years, and the relative risk (RR) of colon cancer among women who ate beef, pig, or lamb every day was 2.49 compared to those who ate it less frequently.[53-55]

A matched case–control study was conducted to prove the hypothesis that eating seafood increases the risk of thyroid cancer. The study concluded that regular users of cod-liver oil, fish liver, or fish sandwich spread have a higher risk of thyroid cancer than irregular and nonusers, and people who eat more fish dinners per week also have a higher risk of thyroid cancer. A population-based case–control interview study was designed to test the hypothesis that dietary iodine or the consumption of goitrogenic vegetables increases the risk of thyroid cancer. A total of 191 histologically confirmed cases (64% females) and 441 matched controls from five ethnic groups in Hawaii were available for analysis. Among women, intake of seafood (especially shellfish), harm ha (a fermented fish sauce), and dietary iodine were associated with an increased risk of cancer.[56,57]

Nidra (sleep)

Although categorical meta-analysis concluded short sleep duration marginally raised cancer risk among Asians and long sleep duration slightly elevated the risk of CRC, neither short nor long sleep duration was substantially linked with cancer risk. To further analyze the reported connection, large-scale, well-designed prospective research is necessary. To prove causation and understand the mechanisms underlying the link between sleep duration and cancer risk, long-term randomized controlled trials are required.[58]

Avyayama (physical inactivity)

A meta-analysis-systemic review covers various survey studies that revealed substantial evidence for a relationship between high physical activity levels and lower rates of bladder, breast, colon, endometrial, esophageal adenocarcinoma, renal, and stomach cancers. RR reductions were from 10% to 20%. The analysis identified moderate to limited relationships between increased physical activity and decreased all-cause and cancer-specific mortality in those with breast, colorectal, or prostate cancer, with RR reductions ranging from 40% to 50%. The updated search included 5 meta-analyses and 25 source publications.

The 2018 guidelines prescribe levels of physical activity that lower risk and enhance survival for various malignancies. More research is needed to determine the relationship between physical activity and less prevalent malignancies as well as survival.[59]

Conclusion

Cancer is a dangerous disease with multiple causes. Many of these variables can be avoided by changing one's diet and lifestyle. Since all diseases stem from imbalanced *Doshas*, maintaining *Dosha* equilibrium is vital. Studies are necessary to determine whether *Ayurveda's* many ideas, such as *Ahara* (diet), *Nidra* (sleep), *Brahmacharya* (celibacy), *Dincharya Rutucharya, Rasayananda* (seasonal regime),

Na-Vegadharana (nonholding of natural urges), and *Yoga* are useful in removing toxins and regulating homeostasis, therefore contributing to increased immunity and warding off cancer. This article gives an overview of the Ayurvedic approach to cancer etiology. This review also asserts the relevance of these etiologies in today's world. While understanding etiologies is critical, it is equally critical to recognize that each person's pattern of exposure to pathogens and *Dhatus* function varies. Studying and understanding etiologies helps to understand the disease and hence helps to prevent it. This accomplishes the primary goal of *Ayurveda*. This study also covers the often overlooked concept of *Nidana Parivarjana* (avoidance of etiologies consumption or practice). Finally, the notion of *Shatkriyakala* (six stages of pathogenesis), that explains the six phases at which a disease can be identified and treated; by comprehending these *Nidanas*, physicians will be able to attack the disease at a very early stage of *Sanchaya* and *Prakopa* (stages of susceptibility and subclinical stages).

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Conflicts of interest

There are no conflicts of interest.

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