

Rising trends of Cancers in Kashmir valley: Distribution Pattern, Incidence and Causes

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Abstract

Enduring health complications are part of older human populations, which are grossly elevated by common food habits and higher use of chemicals or chemical based products. Cancer, a deadliest disease is reason for higher mortality and morbidity on global scale. All types of cancers have been reported in Kashmir valley including the cancers of skin (Kangri cancer), lungs, breast, rectum, stomach, prostate, liver, cervix, esophagus, bladder, blood etc. The causes of such high incidence rates of cancers may be both internal (genetic, mutations, hormonal, poor immune conditions) and external or environmental factors (food habits, industrialization, over growth of population, social etc.). The incidence and mortality of diverse cancers among various geographical regions is important to initiate therapies against the wide range of cancers. The incidence and mortality of various cancers varies among the geographically heterogeneous countries worldwide, some represent the frequent type in geographically heterogeneous regions. This review provides in-depth status of cancers with reference to distribution pattern, incidence and causes in Kashmir valley, a cancer belt of India, having a peculiar cancer profile.

Keywords: Cancer; Mutations; Environmental factors; Kangri cancer; Immune system; Food habits.

Highlights

Our paper is an upto date analysis and evaluation of the cancer epidemiology, causes, distribution and incidence in Kashmir Valley of India owing to its unique culture (including food habits, living conditions etc.) and environment. This paper grossly differs from previous studies in many respects, especially update of cancers from 2011-2020. Current review compares the occurrence and distribution of cancers based on gender in various districts of Kashmir valley; a serene union territory in India. In addition, special focus was attributed to the rising trends of cancers based on incidence, causes and clinical features of some unique indigenous cancers.

Introduction

Cancer is one of the leading causes of mortality and morbidity worldwide [1,2]. Cancer is a malignancy in which the cells grow uncontrollably and spread (Metastasize) to other organs of the body, by bypassing the regulatory checkpoints in cell cycle and dysregulation of cyclin dependent kinases. It is caused by the activation of proto-oncogenes or inactivation of tumor suppressor genes that make a normal cell divide abnormally and grow into a tumor. A number of factors responsible for the development of cancers include viral infections, radiations, tobacco consumption, environmental pollutants and genetic factors [1-6]. Despite the availability of enough treatment options, which include chemotherapeutic agents like Tamoxifen, Angiotensin, Colchicine etc., radiotherapy and immunotherapy [7-10] cancer still remains the global threat. Later fact is due to the reason that most of the cancers remain undetected until the successive stages of metastasis [11-13].

Worldwide scenario of various cancers

Cancers are emerging global health problems throughout the world and is the second leading cause of deaths worldwide exceeded only by cardiovascular diseases [14]. On the basis of previous findings, it is hypothesized that there will be about 1,806,590 new cases of cancers and 606,520 cancer deaths by the end of 2020 [15]. By far, Lung cancer is

the most commonly diagnosed cancer (11.6% of the total cases) and the leading cause of cancer death (18.4% of the total cancer deaths), closely followed by the female breast cancer (11.6%), colorectal cancer (9.2%), stomach cancer (8.2%), and liver cancer (8.2%) for mortality. Lung cancer is the major cause of cancer related deaths in males, succeeded by prostate, colorectal cancer in incidence, liver and stomach cancer for mortality. Breast cancer is the most common and leading malignancy among females, succeeded by colorectal and lung cancer in incidence, and the reverse in mortality; cervical cancer ranks fourth for both incidence and mortality. The incidence and mortality of various cancers varies among the geographically heterogeneous countries worldwide, some represent the frequent type in geographically heterogeneous regions (e.g. liver cancer), while as others show occurrence in certain high-risk regions (e.g. cancers of lip and oral cavity in South Asia, Kaposi sarcoma in Eastern Africa). Because of its high fatality rate, lung cancer is the leading cause of death among men in 93 countries, followed by prostate cancer (46 countries) and liver cancer (20 countries). The incidence of breast cancer among other cancers also shows a dichotomous nature across countries with most frequent cases in the majority (i.e. 154 countries) of countries and with cervical cancer leading in most (28 Of 31 countries) of the remaining countries. The mortality contour among women is more heterogeneous, with breast and cervical cancer as the leading cause of cancer deaths in 103 and 42 countries, respectively, followed by lung cancer in 28 countries. A comparative analysis of the incidence and mortality of different cancers worldwide is shown in Figure 1[16].

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In India, an increasing trend in the incidence of cancer rates is observed with advances in cancer detection and diagnosis. In 2018, over 1.1 million new cancer patients were registered and 0.78 million people have died of cancer [17]. It has been estimated that in India, the tobacco related cancers (TRC) for males are predicted to go up from 1,90,244 in the year 2010 to 2,25,241 in the year 2020 and for female cases, the figures are expected to go up from 75,289 in year 2010 to 93,563 in the year 2020 (Figure 2) [18]. The Union territory of Jammu and Kashmir (reorganized on 31st October 2019) is situated in the northern extreme of India [19] Kashmir valley is located at a very high altitude with a majority of Muslim population, this place possesses unique culture from the rest of the country[20]. Over the past decade, a significant increase in the number of cancer cases has been reported in Kashmir valley. However, the number of cancers diagnosed are predicted to double in the year between 2012-2027 [21]. As per the surveys conducted in Kashmir, it has been shown that among the various cancers, gastric cancer was one of the most common cancers

with about 18.8% prevalence, followed by colorectal cancer, lung cancer, head, neck cancer and breast cancer. An analytic survey depicted the occurrence of various cancers on the basis of gender, the percentage share and occurrence of various cancers As in shown in Figure 3 and Figure 4 [20].

The incidence of various cancers differs across the all districts in Union territory of Jammu and Kashmir with maximum number of cancer patients belonged to the district Srinagar (898; 14.11%), followed by Jammu (853; 13.4%), Baramulla (573; 9.0%), Anantnag (489; 7.7%) and Budgam (452; 7.1%). The district wise incidence of cancer in different districts of Union territory is show in Figure 5 [22].

Scenario of cancers in Kashmir valley

Recent studies regarding the scenario of cancers reveal entirely peculiar existence of cancers in Kashmir valley, in comparison to other states of India. In a study carried out by FA Jan NK et al., 2014, it has

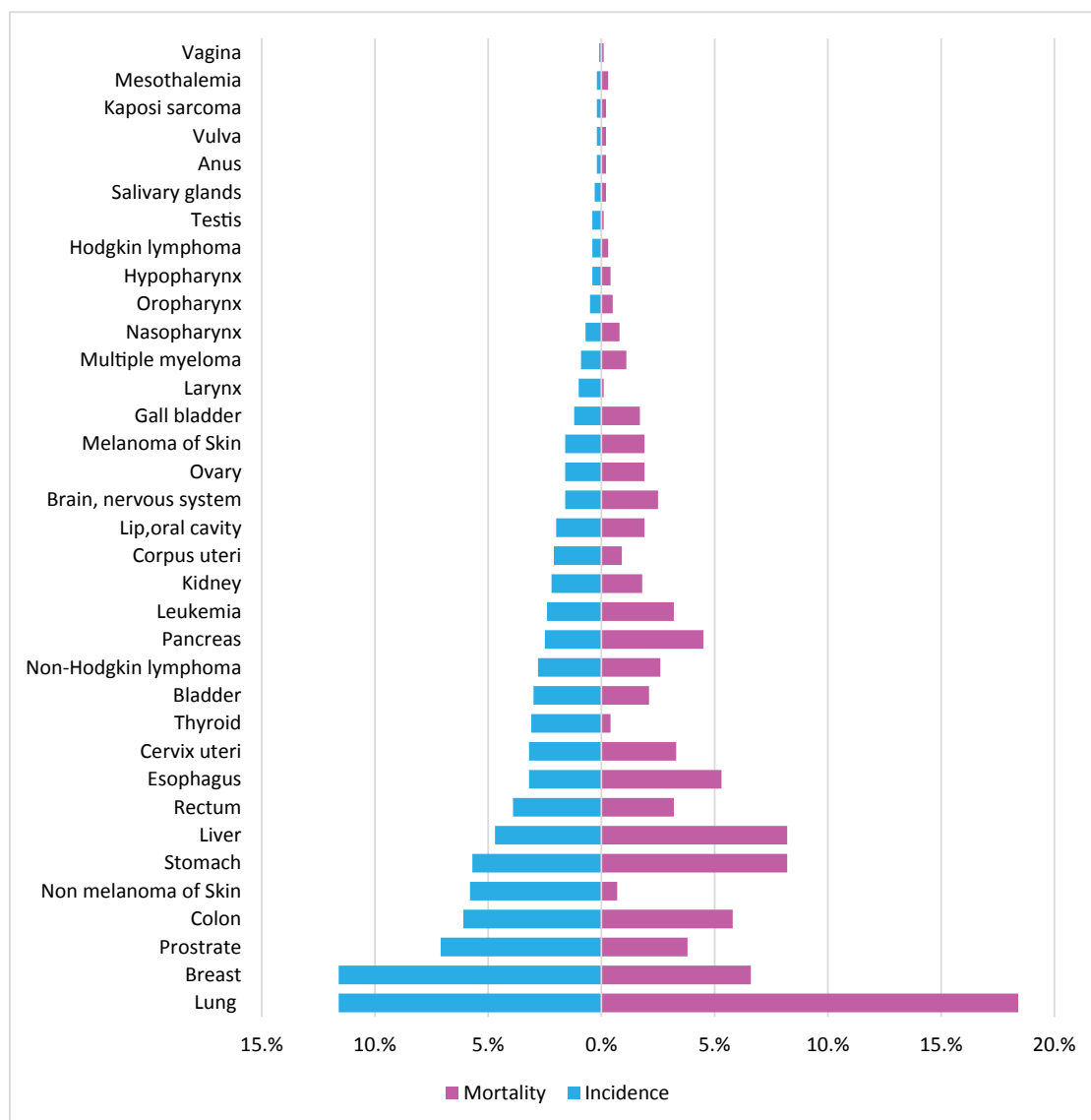
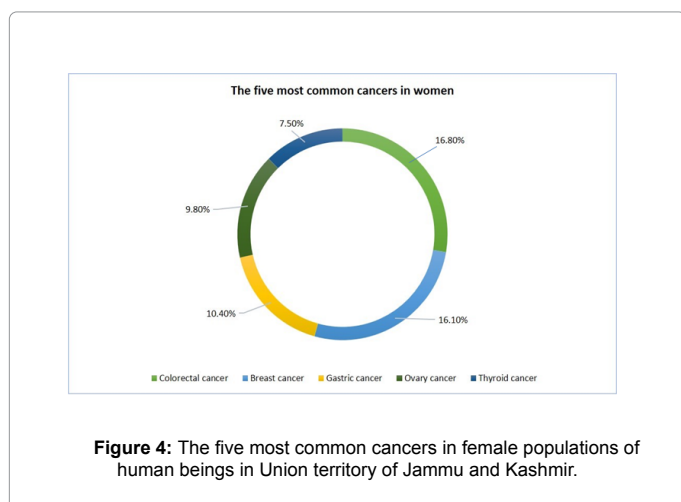
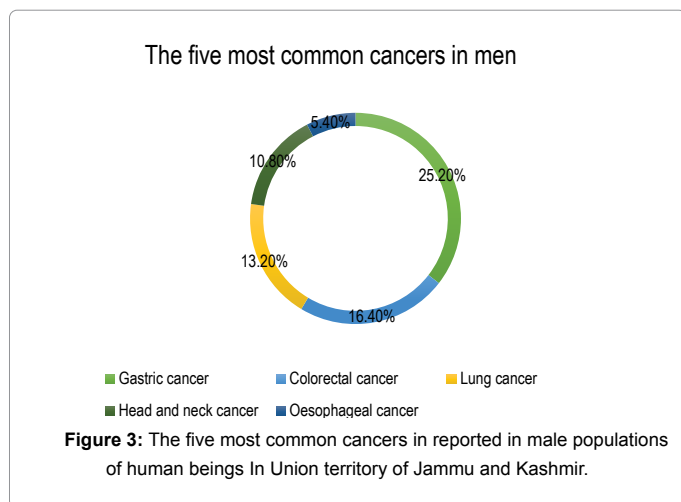
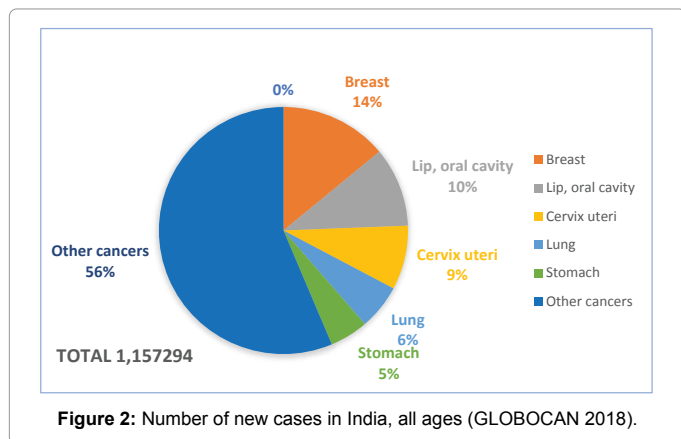


Figure 1: A comparative analysis of the incidence and mortality of different cancers globally (Source: GLOBOCAN 2018).



been found that out of total 24,768 patients with carcinoma reported to Regional Cancer Centre at Sheri Kashmir Institute of Medical Sciences (SKIMS); 15,193 were males and 9,575 were females with majority of patients falling in the age group 65- 69. The study revealed that cancer of esophagus, stomach and lungs have a high incidence both in men and women in Kashmir valley [23]

Pandith et al made a study on “Burden of Cancer in the Valley of

Kashmir” (2012). The studies reveal that stomach cancer is the leading one followed by esophagus and lung cancers. Stomach and lung cancers are frequently found in males, while esophagus cancer tops among women followed by breast cancer [24] In another study, it is revealed that cancer of esophagus was the most frequent type of cancer found in both males and females. The preponderance of esophagus cancer was attributable to the local practice of drinking hot salty tea [25] In addition, the databases on cancer during 2009-2011 prevalence revealed that out of 8,648 cancer patients, which were registered in the hospital, 5,174 were males and 3,474 were females.

Combined gender based studies revealed that the prevalence of esophageal cancers was the mostly found in 1,221 patients with 699 males and 522 females. The possible reason for esophageal cancers may be due to consumption of hot tea called “Noon-Chai” (hot beverage boiled in samovar) both in the morning and in evening time. Later food habit has been proposed to be responsible for the high incidence of esophageal carcinoma in the Kashmiri population and in females the cause of breast cancer is still a mystery [26]. Studies also revealed that esophagus is the leading site of cancer in both sexes, followed by lung, brain, head and neck in males and breast and rectum in females [27]. Studies carried during 2016-2017 reported that 6,359 patients have been diagnosed with different types of cancers in the said union territory. Among all these individuals majority of them were males (4,038 individuals) followed by females (2,321 individuals) [22]. It was found that the leading sites of cancer in males were stomach and lungs in case of females. Majority of the farmer populations in the Kashmir valley are habitual to tobacco smoking, later habit may be possible reason for 70% of throat cancers in males [23]. The studies revealed that gastric cancer is the highly prevalent malignancy in Kashmir. Peculiar life style habits like consumption of hot salted tea and tobacco smoking by hookah (a special device to consume raw tobacco) as well as *Helicobacter pylori* infection are main risk factors causing gastric cancer in the union territory [28].

Inhabitants of Kashmir valley are having distinctive food habits like consumption of large quantity of red meat, sun-dried vegetables, smoked fish, locally prepared vegetable pickles, local salted tea consumed hot (noon chai) in large quantities and tobacco use (hookah) for greater part of the year, which play an devastating role in the development of GIT cancers [29-32]. The ten leading sites of cancers are oesophagus and GE Junction, lung, stomach, colorectal lymphomas, skin, laryngopharynx, acute leukaemias, prostate and brain in males. In females, the leading sites are breast, esophagus and GE Junction, ovary, colorectal, stomach, lung, gallbladder, lymphomas, acute leukemia’s and brain. Oesophagus and stomach alone constituted over 27% of the total cancers [33].

Esophageal cancer

Esophageal cancer is the eighth most commonly occurring cancer and the sixth leading cause of cancer deaths worldwide [34]. Esophageal cancer is the carcinoma of the food pipe which connects the buccal cavity with the stomach [35]. The Kashmir presents a strikingly different picture of esophageal cancer and is the most predominant cancer among both men and women [36,37]. The various elements like nitroso compounds, amines and nitrates present in the local food stuffs causes various GIT cancers in this ethnic Kashmir population [38]. The hookah based smoking practice in the presence of other family members is mostly associated with risk of esophageal cancer [39]. There are two main histological types of esophageal cancer, adenocarcinoma and squamous cell carcinoma [40]. Esophageal squamous cell carcinoma (ESCC) is very common in certain regions in Asia, including Kashmir

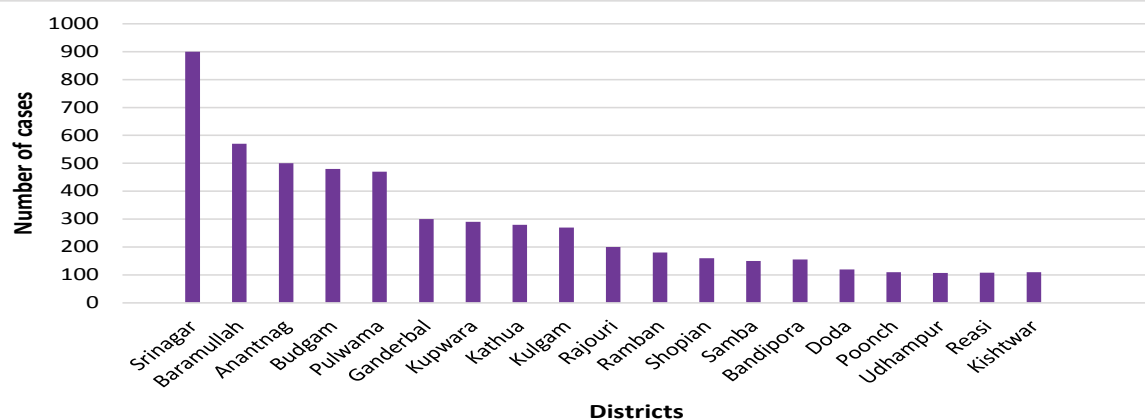


Figure 5: Incidence of cancer in various districts of Union territory of Jammu and Kashmir.

region of India [36].

The etiology of esophageal cancer is very complex and divergent including low socio-economic status [39], [41-46], poor oral hygiene [47-51], contact with animals [52,53], consumption of tea [52-55], tobacco use in different forms, alcohol consumption, and environmental factors [56,57]. In Kashmir, consumption of hot salty tea by local inhabitants is the most important specific food habit. Salt tea contains sodium bicarbonate and common salt, a well-known irritant of gastric epithelium are believed to cause esophageal cancer [58]. Nitrosation of tea extracts results in the formation of high amounts of N-nitrosopiperidine with several unidentified non-volatile N-nitroso compounds which consequently simulates the fasting of human stomach [59].

Kashmiri populations have another specific dietary of drying raw food stuffs in open sun and this dried food is stored and later on consumed in the winter months [57]. Research studies have found that these food stuffs which includes dried fish, vegetables especially Brassica oleracea (haak), red chilies, and a packed bread like oily mixture of spices known as “waer” in Kashmir contain significant amounts of N-nitroso compounds, which results in esophagus cancer [60,61]. Moreover, recent literature on esophageal cancer has indicated the critical role of genetic mutation in the development of diseases [62-67]. A recent genome wide association study (GWAS) in an Asian population indicated that rs2494938 gene variant present in leucine rich repeat fibronectin type 3 domain containing 2 (LRFN2) gene to be associated with three types of cancers including esophageal cancer [68]. Another study has replicated the association of variant rs2494938 of LRFN2 gene with esophageal carcinoma in the population of J&K [69].

Stomach cancer

Stomach cancer is also amongst the first five cancers in the Kashmir having preponderance in male populations (Male:Female-3.17:1). Dietary habits are probably the main reasons for the high incidence of this cancer [36]. In Kashmir valley, gastric cancer incidences are very high and together with esophageal carcinoma accounts for about 60% of all cancers, which is higher than in other parts of the region. It has been reported that the incidence of gastric cancer in Kashmir valley exceeds up to 40% of all cancers, and the incidence is 3-6 times higher than

that at various metropolis cancer registries in India [36]. Consumption of high salt content (including salted tea), distinctive dietary habits and infection with *Helicobacter pylori* may be the possible reasons for the high incidence of this cancer in the Kashmiri population [36,70]. Another risk factors which causes gastric cancer include consumption of adulterated food products like pickled food, high rice intake, spicy food, excess chilly consumption, and intake of food at high temperature, which have emerged as significant risk factors causing stomach cancer in India as well as in Kashmir [36,70-72]. Socio-economic factors and some genetic factors which are distinct to each community have a close association with the gastric cancer load on the community [73,74]. It has also been reported that sun dried vegetables like turnips, tomatoes, bottle gourd, and brinjal, exposing to uncontrolled UV radiations makes the vegetables more prone to aflatoxins and fungi, which may be detrimental to human health [75]. Studies revealed that these preserved and peculiar foods have a significant amount of N-Nitroso compounds, which have great potential to cause cancers [76]. Kashmiri population enjoys a large variety of smoked foods like mutton and beef barbecues popularly called as “Tuji”, which contains large amount cancer causing of N-Nitroso compounds [77]. Heredity diffuse gastric cancer (HDGC) is a rare genetic condition in which the mutated gene (cancer gene) passes from one generation to another, thus making the generation inheriting it more this class of cancer [78].

Colorectal cancer

Colorectal cancer is the 2nd most common cancer among women and the 3rd most common among men in the world [34]. Changing trends in the consumption of food intake by human populations in Kashmir since last few decades is the main cause of colorectal cancer. Epidemiologic studies have showed that the increased risk of colorectal cancer is associated with a diet with a diet high in red meat and animal fat, low fiber diet and low overall intake of fruits and vegetables [79]. Another study has revealed smoking along with other life style choices, such as alcohol and tobacco consumption, obesity and sedentary life style have been associated with increased risk for colorectal cancer [79,80]. Family history of colorectal cancer has also been found with around 10% to 15% of all colorectal cancer cases [81,82]. The risk associated with a family history of CRC depends on the number of affected relatives and the age at diagnosis [83].

Lung cancer

Lung cancer is the most common malignancies throughout world and has diverse clinical presentations and chest complaints in particular. Lung cancer metastasize to every organ in the body, but in isolation, rarely involve skeletal muscles. In one retrospective series, the prevalence of isolated skeletal muscle metastasis (SMM) was seen in 0.16-6% (1). In Kashmir region, lung cancer is reported to be the second most common malignancy [84]. The consumption of tobacco *via*; cigarette smoking, *hookah* smoking, chewing, snuffing is the common cause of lung cancer and is quite prevalent in Kashmir [85]. The consumption of tobacco causes cancers in oral cavity, pharynx, oesophagus, larynx, lungs and urinary bladder. *Hookah* smoking practiced commonly by males and females in rural Kashmir is common risk factor that causes lung cancer [86].

Skin cancer

Carcinoma of the skin in the form of “Kangri” cancer is a common cancer in Kashmir and nearly 50% are of the skin cancer. This type of cancer is a highly aggressive tumor with a propensity for nodal metastasis and is virtually non-existent in the rest of world. The main cause of skin cancer in Kashmir is due to the continuous use of a fire pot (Kangri), during winter season, thus producing a pre-malignant lesion called erythema-ab-ignae. [87,88].

These lesions typically ulcerate and grow exponentially, causing chronic irritation of the skin. Heat represents the main causative factor in instigating the deadly malignancy called the Squamous cell carcinoma, with most commonly affected sites of the lower extremities (thighs) followed by anterior abdomen, with the most common type of presentation resulting in nodulo-ulcerative growth, with history of pain and bleeding [89,90] [91]. Furthermore, the major risk factor for various types of skin cancers *viz.* basal cell carcinoma, squamous cell carcinoma and melanoma is the exposure to ultraviolet light, which is a non-ionizing radiation [92].

Brain cancer

Brain cancer is originating from intracranial tissues and the meninges with degrees of malignancy ranging from benign to aggressive. Benign tumors in the brain can be lethal due to their ability to infiltrate locally, and their propensity to transform to malignancy. The incidence of brain tumors has increased over time and differs according to gender, age, race and ethnicity, and geography [93]. Studies carried at SKIMS (Sheri Kashmir Institute of Medical Sciences) determined the relationship between the patients of primary malignant brain tumors and their occupation on the increasing trend in the incidence of primary malignant brain tumors in orchard farmers and their families in Kashmir. It has been revealed that 90.04% (389 out of 432) patients were orchard farm workers, orchard residents and orchard playing children exposed to the high levels of multiple types of neurotoxic and carcinogenic chemicals for more than 10 years [94]. The residual concentrations of these toxic chemicals in the farm workers have led to a variety of neurological dysfunctions [95,96]. Because of the similarity in the brain biochemistry, the pesticides are particularly neurotoxic to the humans and most lethal are organophosphates, carbamates and ethylene bis-dithio-carbamates [97]. The primary action of the organophosphates and carbamates is irreversibly inhibiting the activity of the enzyme acetylcholinesterase (AChE) that hydrolyses the neurotransmitter acetylcholine in both the peripheral and central nervous systems. This causes accumulation of acetylcholine at cholinergic synapses, leading to overstimulation of muscarinic and

nicotinic receptors and thus neurotoxicity [98,99].

Causes of Various cancers in Kashmir Valley

A number of factors are responsible for the development of cancers, which includes; physical environment (climate, soil and water) and socio-cultural (lifestyle, food habits, alcohol and tobacco consumption, occupation). Among these factors, environmental factors account for about 80% of all the human cancers [100]. while as the rest 10%-20% of all human cancers are associated with dietary factors [101]. With a considerable variation in different types of cancers in areas with different physical and socio-economic setup [102]. The incidence and mortality rate of cancer among Kashmiris have increased due to some unique behavioral and dietary risks including high body mass index, low fruit and vegetable intake, lack of physical activity, tobacco use and lack of regular check-up. There is an alarming increase in cancer incidence in Kashmir valley, mainly because of the changing life style and food habits among the inhabitants that has caused a surge in different cancers especially in esophagus, colon and breast cancers [103] (Table 1).

The cause for cancers can be either both internal factors like inherited mutations, hormones, and immune conditions or environmental factors such as Tobacco, diet, radiation and other infectious agents. In the proceeding section, we have discussed various factors responsible for diverse cancers in Kashmir valley.

Lifestyle Related Factors

Peculiar food habits

Improper diet is one of the main causes of cancers, and the role of diet towards developing cancer varies greatly among different cancer types [115,116]. The heavy consumption of red meat is the main cause of several cancers including gastrointestinal tract and colorectal [117-119], prostate [120], bladder [121], breast [122], gastric [123] and oral cancers [124]. It may be perhaps, due to the production of heterocyclic amines (the most potent carcinogens), during cooking of red meat. Also, pyro-lysates, produced by charcoal cooking or smoke curing of meat exert carcinogenic effects on body cells [125]. PhIP (2-amino-1-methyl-6-phenyl-imidazo [4, 5-b] pyridine) is another potent mutagen present in fried beef expressing 20% of mutagenicity in humans. Food kept in plastic containers turns out to be carcinogenic because bisphenol from the plastic containers gets dissolved and migrates into the food (Figure 6); resulting into the risk of breast [126] and prostate [127] cancers. A low intake of fresh fruits and cooking at high temperatures in Indian dishes may account for low levels of vitamin C; resulting into higher risks of stomach, mouth, pharyngeal, esophageal, lung, pancreas, and cervical cancers [128].

Consumption of high salt content and infection with *Helicobacter pylori* bacteria proves to be another possible reason for the high incidence of gastric cancer in the Kashmiri population [129]. The excess intake of hot salted alkaline tea (Noon Chai), prepared traditionally in a specially designed copper vessel called a ‘samawar’ are some of the distinctive dietary habits for increased risk of gastric cancer in Kashmir valley [28,130]. Other dietary risk factors, which cause gastric cancer, include pickled food, high rice intake, spicy food, excess chilly consumption, and intake of food at high temperature, which have emerged as significant risk factors causing cancers in India and Kashmir valley [28,129,131]. In last few decades, the changing trends in food habits largely accounts for cancer prevalence among population in Kashmir valley. There has been a typical shift from intake

Carcinoma	Risk factors	References
Blood (starts from bone marrow)	Family history, smoking, Down syndrome, ionizing Radiations	[104, 105]
Breast (develops from breast tissue)	Obesity, alcohol consumption, hormone replacement therapy, ionizing radiations	[106]
Colorectal (cancer that affects colon and rectum)	Unhealthy diet, obesity, smoking, alcohol use	[107]
Lung (uncontrolled cell growth in tissues of lung)	Tobacco smoking (80%), genetic, radon gas, air pollution	[108-110]
Ovarian (cancer that forms in ovary)	Never having children, obesity, genetic factors, fertility medication	[111]
Skin (arise from skin)	Light skin, poor immune function	[112]
Stomach (developing from the lining of stomach)	<i>Helicobacter pylori</i> (65%- 80%), smoking	[113, 114]

Table 1: Shows different types of carcinomas along with risk factors.

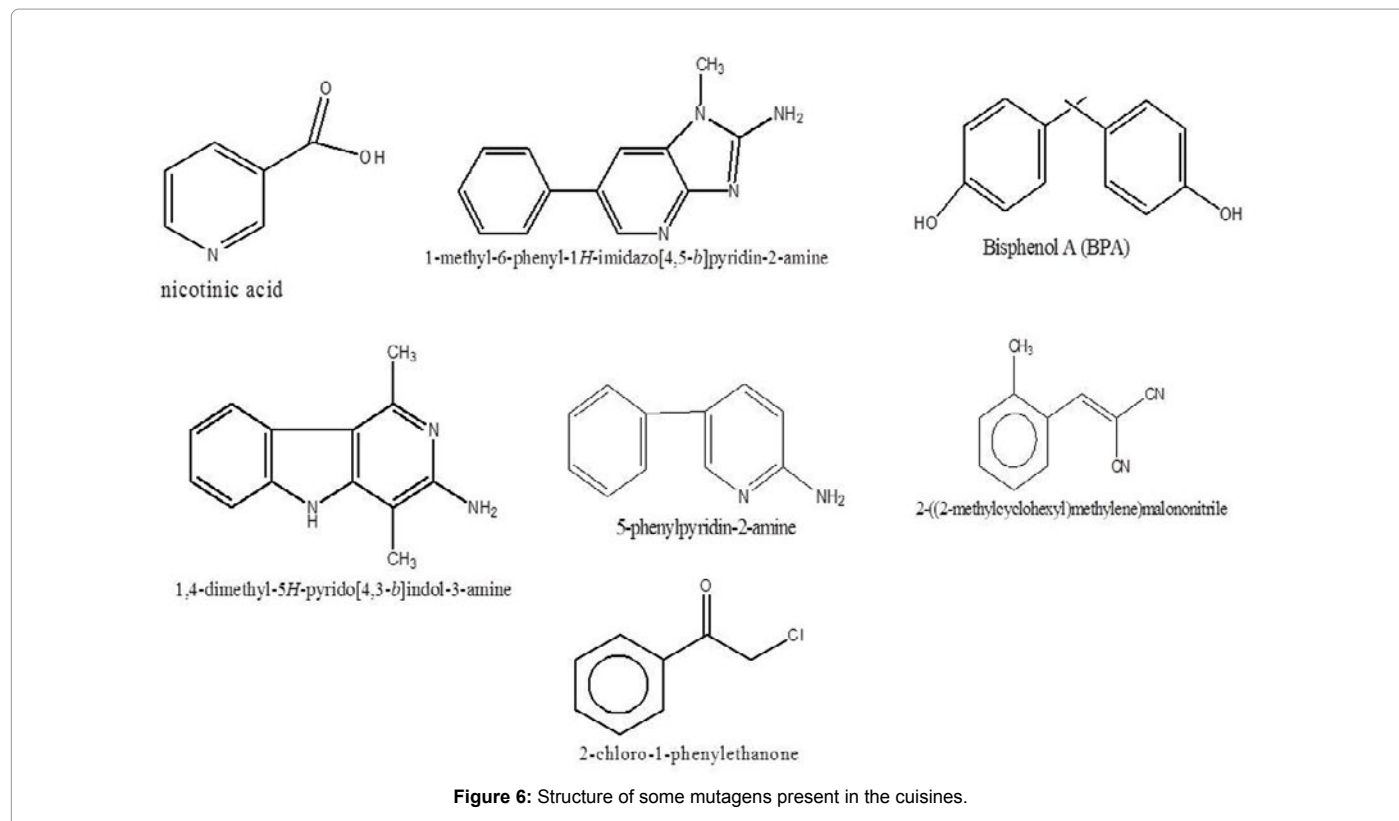


Figure 6: Structure of some mutagens present in the cuisines.

of traditional food which was rich in complex carbohydrate to more of simple carbohydrates has increased the risk of obesity, increasing the incidence of colorectal cancer in many countries [132].

Smoking and alcohol

The consumption of tobacco through smoking, hookah smoking, chewing, snuffing etc. is also the foremost cause of cancers. The various cancers produced by the use of tobacco are of oral cavity, pharynx, esophagus, larynx, lungs and urinary bladder. Smoking is the most common factor responsible for lung cancer [133]. Use of tobacco in different forms like cigarette smoking, hookah, and snuff is quite prevalent in Kashmir. Smoking in the valley is a male pastime; the women do not generally smoke. Hookah smoking (a special cigar using raw tobacco) practiced commonly by both, the males and females in rural Kashmir is another risk factor that causes lung cancer [134]. In Kashmir, cigarette smoking and hookah smoking are the most popular form and are largely responsible for passive smoking of other family members, especially during winter months, when soot, smoke, and fumes from kitchens and various types of heating pollute the indoor air in ill ventilated and overcrowded dwellings [134]. Chronic damage due

to alcohol consumption can lead to liver cirrhosis and the development of hepatocellular carcinoma, a form of liver cancer [135]. The World Health Organization (WHO) has classified alcohol as a Group 1 carcinogen and is the major causes of colorectal cancer [136-139], but in Kashmir valley only a rare part of population is addicted to the consumption of alcohol.

Stress as a cause of cancer

Cancer and stress both involve an enormous complexity, heterogeneity and multifactorial pathogenesis. It is well known that cancer growth involves the microenvironment (TME), which contains a myriad of cells and pathways, which include cytokines, growth factors and adhesion molecules. Initially, the tumor cells are in symbiosis status, but on contact with growth factors and nutrients from the host tissue, it produces angiogenic factors and form new vessels changing the tumor microenvironment, thus leading to the invasiveness and "tumor escape" to other tissues [140]. Stress induced cancer mediators like catecholamines, cortisol, hormones; neurotransmitters impair the immune system and impact on mechanisms of DNA repair and metastatic spread [141-144] Also, stressed individuals are more

likely to develop an addiction towards tobacco smoking and alcohol consumption than stress-free individuals [145]. Since the partition of India in 1947, Kashmir has been facing political conflicts and insecurity [146]. The stressful life conditions are on a rise in the valley due to the loss of human life in the conflicts, and the psychological wellbeing of the population has also been affected by natural disasters like 7.6 Mw magnitude earthquake in 2005 and floods in 2014 [147-150]. In 2015, a survey conducted by MSF in collaboration with the Department of Psychology, University of Kashmir and NIMHANS on mental distress in ten districts of valley [151,152] showed a strong link between vulnerability to multiple traumatogenic events and symptoms of Major Depressive Disorder (MDD), Generalized Anxiety Disorder (GAD) and Post-traumatic disorder (PTSD) [152]. Distressingly, 12% of survey has reported existence of stress among Kashmiri population, due to the death of their close relations in violent conflicts [153]. The English surgeon, Guy (1759), reported, "Breast cancer seems more common in depressed, phlegmatic and melancholic women". Burrows in 1783, wrote about the effects of stressful emotion on the body's physiological states: "the painful passions of the mind in the long run weaken the blood circulation and predispose to cancer" [154,155]. Therefore, existence of stressful conditions in Kashmir represents another cause of cancer among this very population.

Environmental Factors

Radiation

About 10% cancers are caused by both ionizing and non-ionizing radiations [156]. On frequent exposures to high-energy radiation like ultraviolet radiation (present in sunlight), x-rays, and gamma radiation there is a risk of developing cancer. The more potent ultraviolet (UV) radiation coming from the sun, sunlamps, and tanning booths is known to cause early aging of the skin that can lead to skin cancer. Moreover, the other major sources of cancer include radiations from radioactive compounds and pulsed electromagnetic fields. A number of cancers induced by exposure to the adequate doses of these carcinogenic radiations include thyroid, skin, leukemia, lymphoma, lung and breast carcinomas. There is a high risk of attainment of breast cancer among girls at puberty after chest irradiation of X-rays, for diagnostic and therapeutic purposes. Furthermore, the major risk factor for various types of skin cancers *viz.* basal cell carcinoma, squamous cell carcinoma and melanoma is the exposure to ultraviolet light, which is a non-ionizing radiation.

Environmental pollution

Air and water pollution are the results of biological, biochemical and atmospheric particles, which cause damages to our living environment. Air pollution is a significant risk factor for respiratory infections, cardiac disease and lung cancer. The main cause of air pollution includes particulate matter, damaged ozone, nitrogen dioxide, sulphur dioxide, carbon dioxide, carbon monoxide, ammonia, radioactive decay of radon gas, methane, hydrofluorocarbons and chlorofluorocarbons produced combustion of fuels in automobiles and several industrial processes. Almost 3.5 million deaths are caused by both indoor and outdoor pollution worldwide [157]. The water pollutants such as, oil, plastics, detergents, chloroform, petroleum, polychlorinated biphenyl, fertilizer, sulphur oxide, pesticides and trichloroethylene are also responsible for various human diseases including cancer [158] An increased risk of cancer has been observed in people using chlorinated water for drinking purposes since decades. N-Nitroso compounds that is mutagenic in nature, are formed from nitrates present in drinking water and increase the risk of lymphoma, leukaemia, and colorectal cancer

and bladder cancers [156] Furthermore, Tear gases such as o-chloro-benzyl-idenemalononitrile (CS), dibenzoxazepine (CR) and phenacyl chloride (CN) are used for riot control (Figure 7), which stimulate corneal nerves of the eye to cause tearing [159-163] CS gas in tear gas is under strict analysis, because it is applied as a mixture with methylene chloride, that is a human carcinogen [161]. It has been seen that severe exposure to methylene chloride primarily dampens the central nervous system and several studies has shown its carcinogenic effects on animals, for example after chronic inhalation of this compound at high concentrations caused liver, lung and benign mammary gland tumors in mice and rats [164]. Therefore, proving to be as another evident risk factor for developing cancer in Kashmiri population.

Infections

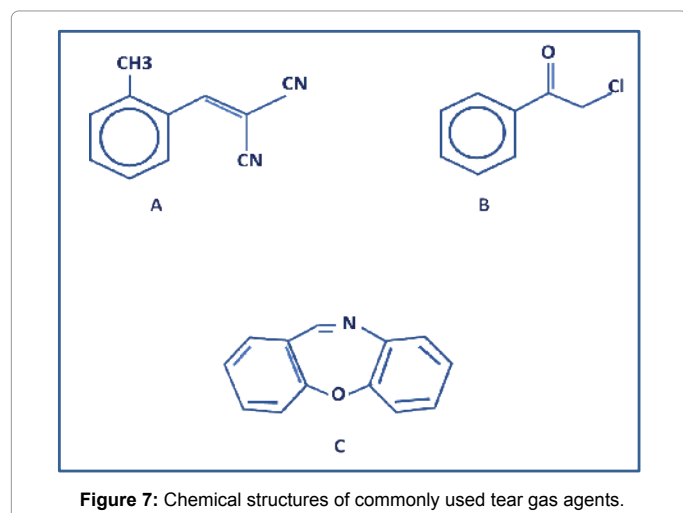
It has been known from quite a long time, which cancer can be caused by various infectious agents. Today, many experimental and epidemiological studies have also indicated that a variety of infectious agents constitute one of the main causes of cancer worldwide [165]. Viruses represent the principle cause, with at least eight different viruses known to be associated with particular tumour types, with varying degrees of certainty. Other infectious agents involved in carcinogenesis are parasites and one bacterium [166,170] (Table 2).

The various infectious agents that cause cancer include viruses (Hepatitis B and C viruses, Human papillomavirus, Epstein-Barr virus, Human immunodeficiency virus, Human T-cell lymphotropic virus, Human herpes virus B), bacterium (*Helicobacter pylori*) and Parasites. It has been estimated that chronic persistent infection with Hepatitis B virus (HBV) causes 60% of primary liver cancer worldwide and 67% of cases in developing countries [165], with Hepatitis C virus (HCV) representing the major cause of parenterally transmitted hepatitis worldwide. About 25% of cases of liver cancer in the world are attributable to HCV [166].

Human papillomavirus (HPV) are known to infect the genital tract [168]. Epstein-Barr virus (EBV) has a causal role in nasopharyngeal carcinoma and sinonasal angiocentric T-cell lymphoma. The infection of EBV is associated with non-Hodgkin lymphoma mainly in patients with congenital or acquired immunodeficiency [170] The role of Human immunodeficiency virus (HIV) is probably as an immunosuppressive agent, which also enhances the risk of cancers [168,170]. Among others, Human T-cell lymphotropic virus (HTLV-1) is the main etiological factor in adult T-cell leukaemia/lymphoma. This disease occurs almost exclusively in areas where HTLV-1 is endemic [157,169]. Human herpes virus 8 (HHV-8) infections appears to be common agent in Kaposi sarcomas [171]. *Helicobacter pylori* the main cause of gastritis and peptic ulcer; infection may be lifelong if not treated with antibiotics [172]. Parasitic infections are strongly associated with cancers and include *Schistosoma haematobium* (squamous cell carcinoma of the bladder) and the liver flukes, *Opisthorchis viverrini* and *Clonorchis sinensis* (cholangio carcinoma) [165,167]. However, these infectious agents are cosmopolitan; these may also represent another risk factor for cancer in this very population.

Occupational carcinogens

The first reports of associations between risk of cancer and employment in particular occupations appeared during the 18th century, however, the majority of studies establishing a link between an increased risk of cancer and a particular working environment were published between 1950 and 1975 [173]. As a result of hasty global industrialization and formation of local industries in developing



of different immune checkpoint inhibitors, such as anti-CTLA-4 and anti-PD-1 have demonstrated enhanced efficacy, with some challenges yet to be met regarding the proper dosage and the identification of more effective combinations. Furthermore, the combination of cancer immunotherapy with other treatment options like radiation therapy, chemotherapy etc. may also prove to be effective [189-191], as various preliminary evidences have shown synergistic effects of these strategies in combination with immunotherapy [189-192].

Conclusion

Causes of various cancers in the Kashmir valley have not been well researched, and no such large population based epidemiological studies have been carried so far. There is an increasing risk of cancer mortality rate among human populations of Kashmir valley due to some leading behavioral and dietary habits, including high body mass index, low fruit and vegetable intake, lack of physical activity, tobacco use, stress and lack of regular check-up. The changing life style and food habits among the people had caused surge in all the cancers especially in Lung, GIT and blood cancers. The rise in cancer cases is also due to intake of spicy food, changing dietary habits and consumption of bulk of contaminated food items available in the market. There is massive adulteration in mass consumption food items, which aggravates the problem further. Smoking related tumors have a high incidence in the valley, such as lung cancers. Due to increasing smoking rates in children and young adults, the incidence of such cancers may further rise in near future.

The overall incidence of cancer in Kashmir valley shows an increasing trend. Future studies need to be focused on sources and causes of various cancers that may improve our understanding of risk factors for these malignancies in this region and help us eradicating the same.

Conflict of Interest

The authors declare no conflict of interest, financial or otherwise.

Authors' Contributions

MAM initiated the study, designed the plan and edited the manuscript. HQ, BAB UM in the author contributions. and MAM wrote the manuscript and designed the figures and tables. MAM, HQ and BAB reviewed the manuscript and arranged the references. MAM read and approved the final manuscript.

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Infectious agent	Cancer site
1. Viruses	
HPV	Cervix and other sites
HBV, HCV	Liver
EBV	Lymphomas and naso-pharyngeal carcinoma
HHV-8	Kaposi sarcoma
HTLV-1	Leukemia
2. Bacterium	
<i>H. pylori</i>	Stomach
3. Parasites	
<i>Schistosoma haematobium</i>	Bladder or intestines
Liver flukes <i>Opisthorchis viverrini</i> <i>Clonorchis sinensis</i>	Cholangio carcinoma

Table 2: Various types of cancers caused by infectious agents worldwide.

countries, the occupational exposures to carcinogens is increasing at a rapid pace [174]. Furthermore, in farming the utilization of pesticides and fertilizers and exposure to insecticides, Fungicides, Chemicals, Dust (organic and inorganic), Manure in daily routine works has shown evidence of gastric cancer risk among the farmers and their wives [175,176]. It represents another risk factor with no exception in Kashmir.

Immunotherapy as a hope for cancer treatment'

Cancer is a genomically deranged malignancy [177] from the past years, surgery, radiotherapy and chemotherapy has been the only anti-cancer treatment options available [178,179]. Despite the therapeutic efficacy of these strategies for removal of primary tumors, disease recurrence poses a serious problem of cancer metastases [180,181] consequently making it necessary to look into the alternative treatment options to eradicate the tumor causing cells [182]. Cancer immunotherapy represents a promising strategy to eliminate the deadly malignancy [180,183-186] Immunotherapy uses a person's own immune system against cancer [180,183-186]. As a field, cancer immunotherapy is proving extremely effective in a number of different ways, such as Immune blockade therapy, chimeric antigen receptor (CAR) T-cell therapy, cancer vaccines and monoclonal antibodies [187,188] More recently, various combinatorial therapeutic approaches are showing enhanced efficacy in combating cancer, for example, the combination

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