Cancer Risk Factors: A Critical Review

A project submitted

by

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Dedicated to my parents who encourage me in every step of my life and give me the strength to complete my project on time.

CERTIFICATION STATEMENT

This is to certify that this project titled “Cancer Risk Factors: A Critical Review” submitted for the partial fulfillment of the requirements for the degree of Bachelor of Pharmacy from the Department of Pharmacy, BRAC University, constitutes my own work under the supervision of Dr. Mohammad Zulfiquer Hossain, Associate Professor, Department of Pharmacy, BRAC University and that appropriate credit is given where I have used the language, ideas or writings of another.

Signed,

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Countersigned by the supervisor,

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ABSTRACT

The global burden of cancer cases has been estimated to rise from 14.1 million to 23.6 million between 2012 and 2030. Many genetic and environmental risk factors are likely to induce the incidence and mortality rate and hence, may further influence the frequency of cancer occurrence. The risk factors that contribute to the risk of developing cancer mainly comprise of genetic changes, family history, age, tobacco/smoking consumption, alcohol intake, air pollution, radiation, sunlight, obesity and poor diet. Often some vulnerable factors may not be avoided, but through the limitation of exposure to such causative agents, it may be possible to lower the risk of developing cancer to some extent. The most widely recognized cancers worldwide that includes lung, female breast, bowel, prostate accounts for 42% of all new cases. The cases were found to be higher in the low and medium human development index (HDI) countries than in high and very high human development index (HDI) countries. So far, very few studies have been conducted to identify the risk factors which might cause cancer. The purpose of this review article is to summarize and evaluate current literature on cancer risk factors as well as to point out gaps on the existing knowledge about cancer causing factors among people and recommend studies to be performed efficiently to discover any new risk factors involved.

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List of Acronyms

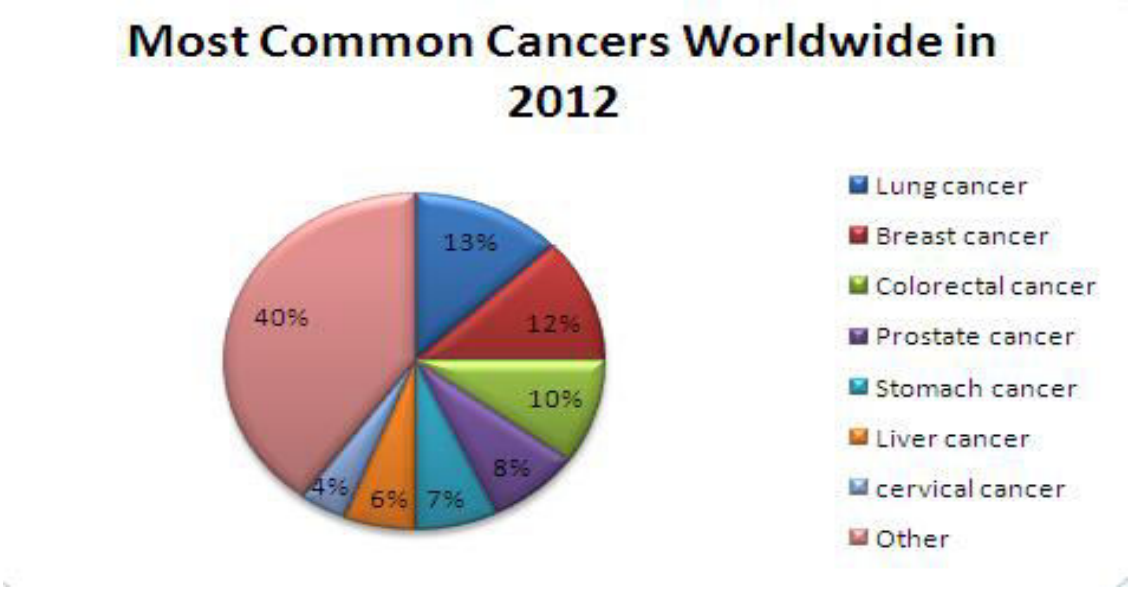
LMIC	Low and medium income countries
HDI	Human Development Index
MDR	More Developed Region
LDR	Less Developed Region
PAH	Polycyclic Aromatic Hydrocarbons
PeCa	Penile Carcinoma
TAMs	Tumor Associated Macrophages
NTP	National Toxicology Program
KS	Kaposi Sarcoma
KSHV	Kaposi sarcoma associated herpes virus

Chapter 1
Introduction

1.1 Background

1.1.1 Cancer Prevalence

Cancer is considered as one of the most significant causes of morbidity and mortality worldwide. Every year cancer incidence and mortality have been increasing exponentially. In 2012, 14.1 million new cases of cancer were diagnosed worldwide and among them 7.4 million (53%) were males and 6.7 million (47%) were females (Cancer Research UK, 2014). On the other hand, in another study, it was found that 32.5 million men and women survived cancer for five years where most of them had been diagnosed with breast (females only), bowel or prostate cancer. Moreover, it has been estimated that the incidence rate of 14.1 million new cancer cases will rise to 23.6 million by 2030. The number of cases will be then 68% more than it was in 2012 and the rates are higher in low and medium human development index (HDI) countries than in high and very high human development index (HDI) countries. In 2012, the most widely recognized cancers worldwide, namely lung, female breast, bowel and prostate cancers represented more than four out of ten (42%) of all new cases(Cancer Research UK, 2014). The following diagram illustrates the incident rates of the most common cancers worldwide.



Source: GLOBOCAN 2012

Figure 1.1: Most Common Cancers Worldwide in 2012

Among all the cancers diagnosed worldwide in 2012, the cancers that were found to occur most commonly in female and male are shown in the Table 1.1 –

Table 1.1- Common cancers among female and male according to the data of 2012

Gender	**Name of the cancers**
Female	Breast cancer Stomach cancer Colorectal cancer Lung cancer
Male	Lung cancer Prostate cancer Colorectal cancer Stomach cancer Liver cancer

(Centers for Disease Control and Prevention, 2016)

In 2012, the mortality incidence from cancer was 8.2 million worldwide and separately for males and females the numbers were 4.7 million and 3.5 million respectively. Lung cancer is considered the most common cause of death in males and accounts for 24% of cancer deaths in males. Other types of cancer that are responsible for death in males are liver, stomach bowel and prostate cancer , representing for 11%, 10%, 8%, and 7% of the male deaths correspondingly.

Additionally, for female, breast cancer is the most well-known reason to contribute to mortality and represents15% of cancer deaths in female. Furthermore, liver, bowel, cervical and stomach cancers are the other most frequent reasons for death resulting from cancer in females around the world, representing 14%, 9%, and 7% of female respectively (Cancer Research UK,2014).

Bangladesh, with a population over 142 million people, is the ninth most densely populated country in the world. The number of cancer patients in Bangladesh is around 15 lakh. However, every year almost around 2 lakh patients are being newly diagnosed with cancer. For males, lung cancer and mouth-orophranyx cancer are the most prevalent one. Other types of leading cancers are esophageal cancer and stomach cancer. Cervical cancer and breast cancer are ranked as the most common cancer for female. Another cancer types such as mouth and oropharynx, lung cancer and esophagus cancer can also affect women. (S. M. Hussain, 2013).

According to the Bangladesh Bureau of Statistics (BBS, 2014), cancer is considered the 6th leading cause of death in Bangladesh. According to IARC (International Agency for Research on Cancer) (2008), the pre-eminent reasons of death due to cancer in Bangladesh vary depending on gender and age. The people aged more than 30 years are more likely to suffer from oral, pharynx and laryngeal and lungs cancer and a recent study of WHO shows that there are 49000 oral, 71000 pharynx and laryngeal and 196000 lungs cancer cases in Bangladesh. Most prevalent cancers in Bangladesh for men are mouth and oropharynx cancer and for women are cervix uteri cancer and breast cancer. (S. A. Hussain & Sullivan, 2013)

In Bangladesh, we do not yet have population based tumor registries. According to the annual report of National Institute of Cancer Research Hospital (NIRCH) in 2007, listed top five cancers among men, women and both sexes are as follows:

Table 1.2- Top five cancers according to NIRCH in 2007

Men (%)	**Women (%)**	**Both sexes (%)**
Lung (25.5)	Breast(25.6)	Lung (17.3)
Lymphoma (7.4)	Cervix uteri(21.5)	Breast(12.3)
Esophagus(5.9)	Esophagus (3.4)	Cervix(9.1)
Larynx(5.4)	Lung(5.6)	Lymphoma(6.0)
Stomach(5.1)	Lymphoma (4.1)	Esophagus(4.6)

NIRCH (National Institute of Cancer Research Hospital)

As reported by the data of 2012, 471(12%) pediatric patients were admitted in NIRCH. A table is given at below showing the number of patients suffering from the top five pediatric cancers at NIRCH in 2012.

Table 1.3-Top five pediatric cancers attending NIRCH in 2012

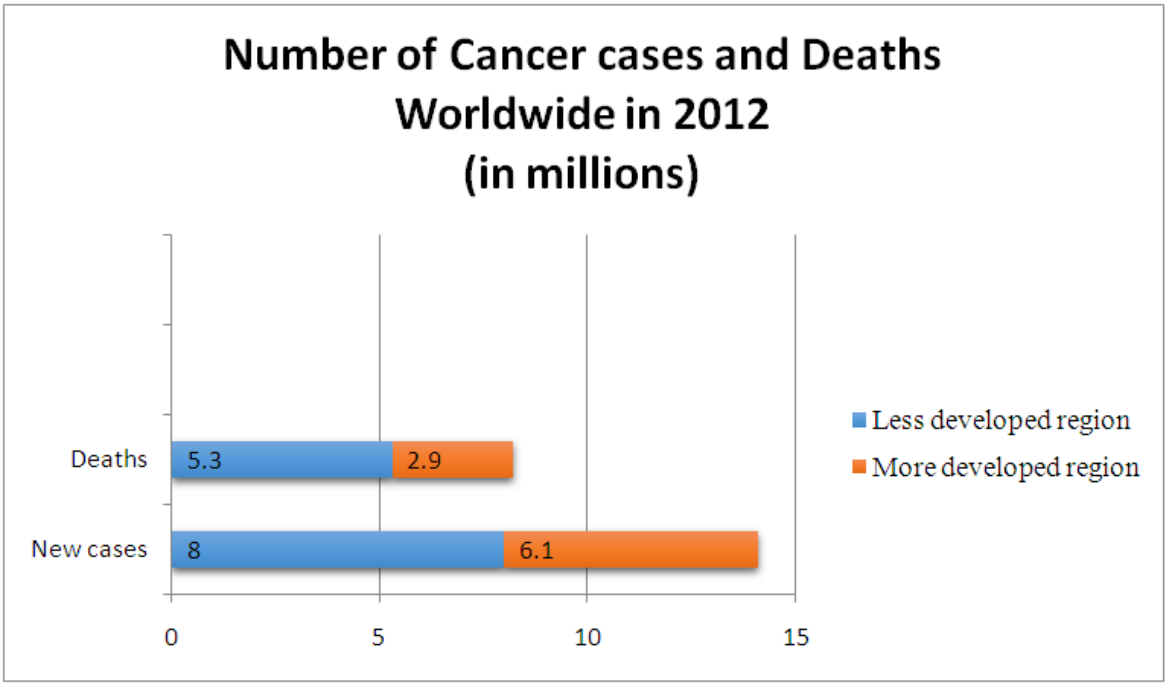
Name of the cancer	**Number**
Retinoblastoma	74
Ewing's sarcoma	29
Osteosarcoma	29
Rhabdomyosarcoma	28
Nephroblastoma	21

NIRCH (National Institute of Cancer Research Institute)

(Uddin, Khan, Islam, & Mahmud, 2013)

1.1.2 Trends

In 2008, there were an estimated 12.7 million cancer cases and 7.6 million cancer deaths among the world's 6.8 billion people. However, lung, prostate, colorectal, stomach, liver and esophagus cancer, which are being considered as the most common cancers for men, accounted for 63% of cases. On the other hand, for female the most common cancers are breast, colorectal, cervix, lung, stomach and uterus collectively accounted for 60% of cases. According to GLOBOCAN, by 2012, the estimated incidence cases were rise to 14.1 million and the deaths were 8.2 million due to cancer. It is predicted that the world population will rise to 8.3 billion by 2030 and demographic impacts alone will offer ascent to an expected 21.4 million cancer cases and 13.2 million deaths because of cancer. Thus between 2010 and 2030, the yearly incidence cases are predicted to rise from 5.7 to 7.4 million in more developed region where the rate will be much larger in LMICs (low and medium income countries) rising from 7.5 to 12.9 million. Apart from that around 1.9 million extra incident rate will be in china, 0.6 million in Africa, 0.7 million in Latin America and Caribbean, 0.7 million in India and 1.6 million in whatever is left of Asia.(McCormack & Boffetta, 2011



Source: GLOBOCAN 2012

Figure 1.2: Number of Cancer cases and Deaths Worldwide in 2012

1.1.3 Cancer Types

Cancers are grouped in two ways: by the kind of tissue in which the disease begins and by the essential site, or the area in the body where the tumor is initially created.

1.1.4 Histological classification

From a histological angle, there are many diverse growths which are gathered into six noteworthy classifications: Carcinoma, Sarcoma, Myeloma, Leukemia, Lymphoma, Mixed types

Carcinoma

The harmful neoplasm of epithelial source or tumor of the inner or external lining of the body is known as carcinoma. It represents around 80 to 90% of all cancer cases. Carcinomas are partitioned into two subtypes: adenocarcinoma, which occurs in an organ or gland and squamous cell carcinoma which starts in the squamous epithelium. Ordinarily, adenocarcinoma happens in mucus membranes and presents as a thickened plaque-like white mucosa. They are frequently dispersed effectively through the delicate tissues where they happen. On the other hand, squamous cell carcinomas happen in numerous areas of the body. Most carcinomas affect organs or glands for emission, for example, the breasts which produce milk or the lungs which emit mucus or prostate or colon or bladder.

Sarcoma

Sarcoma tumors occur in the connective tissues or supportive tissues like bone, muscle, cartilage and tendon. Osteosarcoma is a bone cancer which falls under sarcoma. Some examples of sarcomas are mesothelial sarcoma or mesothelioma (membranous lining of body cavities), angiosarcoma or hemangioendothelioma(blood vessels), chondrosarcoma (skeletal muscle), rhabdomyosarcoma (skeletal muscle), leiomyosarcoma (smooth muscle), liposarcoma (adipose or fatty tissue), myxosarcoma (primitive embryonic connective tissue), glioma or astrocytoma (neurogenic connective tissue in the brain) and mesenchymous or mixed mesodermal sarcoma (mixed connective tissue type).

Myeloma

Myeloma refers to those malignancies that begin in the plasma cells of bone marrow. The plasma cells create a portion of the proteins found in blood.

Leukemia

Leukemia refers to the cancer of bone marrow. The word leukemia means “white blood” in Greek. This disease mainly results from the overproduction of immature white platelets. These immature white platelets cannot do their jobs and make the patient susceptible to infection. Leukemia additionally affects red platelets and can bring about poor blood coagulation and drowsiness because of anemia. Some examples of leukemia are lymphatic, lymphocytic, or lymphoblastic leukemia (malignancy of the lymphoid and lymphocytic blood cell series), granulocytic or myelogenous leukemia (malignancy of the myeloid and granulocytic white blood cell series) and polycythemia vera or erythemia (malignancy of various blood cell products, but red cells prevailing.

Lymphoma

Lymphomas mainly grow in the nodes of the lymphatic network, a system of vessels, hubs, and organs (particularly tonsils, thymus and spleen) which clean natural body liquids and produce pathogen battling white platelets or lymphocytes. The lymphomas are again sub-classified into two classes, Hodgkin lymphoma and Non-Hodgkin lymphoma. In Hodgkin lymphoma, the Reed-Sternberg cells are present which is actually absent in Hodgkin lymphoma.

Mixed Types

This sort of cancers might arise from inside one class or from various overlapping classes. A few illustrations are carcinosarcoma, teratocarcinoma, mixed mesodermal tumor and adenosquamous carcinoma. (Mandal. 2012)

1.1.5 Classification by site of origin

Depending on the site of initiation of cancer in the body, it can be classified by following types- breast cancer, ovarian cancer, cervix cancer, esophageal cancer, colorectal cancer, pancreatic cancer, stomach cancer, liver cancer, gall bladder cancer, lung cancer, skin cancer, kidney cancer etc.

1.2 Rationale of the study

Cancer is a class of diseases characterized by abnormal growth of cell. Every year cancer morbidity and mortality are increasing expeditiously. There are many more risk factors including genetic and environmental risk factors that result in the rise of cancer. There have been reviews about cancer and their risk factors but these are not extensive. Most of the reviews are cancer specific where there is a need of overall information regarding all cancer and the risk factors. Thus the rationale of the study is to integrate a global knowledge about cancer risk factors as well as to identify gaps in knowledge and evaluate current method for identifying risk factors. This study has not been adequately done previously. Another rationale for writing this review article is to target local audience or local expert to fill those gaps and improve the knowledge of this field.

1.3 Aim and objectives of the study

The aim of the study is to present a critical review of hereditary as well as environmental factors that contribute to carcinogenesis. In addition, the objectives of the study are to summarize current literature on cancer risk factors, evaluate current methods for identifying risk factors as well as to find gaps in knowledge and to recommend new studies which will make the process of identifying risk factors more rapid and efficient.

Chapter 2

Cancer risk factors

Cancer risk factors

There are certain factors that are linked to the development of cancer which are called risk factors. There are mainly two risk factors including genetic and/or hereditary and environmental risk factors that result in the rise of cancer

2.1 Hereditary/Familial factors

Breast cancer: One of the most important risk factor behind the development of breast cancer is gene mutation (5to10%) or family history (20%) (Ava Kwong , 2016). Women who carry the defective BRCA1 and BRCA2 gene are supposed to have 5 to 20 fold increased risk of developing breast cancer (Allison W. Kurian, Alexander Miron, &Carmel Apicella, 2011). TP53 and PTEN genes also have a significant role in breast cancer development. Some of the other genes that researchers have found to contribute in breast cancer risk are CASP8, FGFR2, TNRCP, MAP3K1, rs4973768, LSP1respectively. On the other hand there are some rare genes that can also have faults and increase breast cancer risk. They include ATM, CHEK2, BRIPI, PALB2 (Ava Kwong, 2016; Cancer Research UK, 2014)

Cervical cancer: Cervical cancer which can also occur due to genetic factors is the third most common cause of death in women and second highest in some developing countries. Patients who carry one or two copies of p21gene polymorphism (rs1801270) and rs2048718BRIP1 gene polymorphism were less likely to have cervical cancer than carriers of homozygous genotype of ancestral allele (Gabriela A. Martínez-Nava1 &Kirvis Torres-Poveda4, 2016).

Colorectal cancer: Approximately, 25-30% of colorectal cancer emerges because of the genetic susceptibility along with 5-10% because of germ line mutations which include Lynch syndrome, Familial Adomatous Polyposis, MUTYH-associated polyposis, NTHL1-associated polyposis, Peutz-Jeghers syndrome, Juvenile Polyposis syndrome, and certain hamartomatous polyposis conditions. All of these syndromes have a high risk of development of CRC. Regardless of this, an expansive part of the heritability of colorectal cancer is still not identified. Some studies show the involvement of LRP6 and PTPN12 as novel candidate genes for CRC susceptibility (Jasperson, Tuohy, Neklason, & Burt, 2010;

Richarda M. de Voer1, R. Mensenkamp1, Marleen Kets1, Marloes Tychon1, &Nicoline Hoogerbrugge1, 2016) .

Lung cancer: Personal or family history plays an important role of risk factors in developing the lung cancer. Patients who are the carriers of TP53 germ line mutation and also smokers are three times more likely to develop lung cancer than non-smokers. One report showed a marker on chromosome 15 which is associated with lung cancer and this marker contains three genes for subunits of the nicotine acetylcholine receptor. People contain one copy of this marker have 30% and those with two copies of this marker have 70-80% increased risk for developing lung cancer, respectively. (Cecilia Zappa, 2016)

Pancreatic cancer: In spite of the fact that the event of pancreatic cancer appears to be sporadic, it has been demonstrated that 5-10% of pancreatic cancer patients have hereditary factors. Inclination to the inherited pancreatic cancer falls generally into three groups. The primary comprises of inherited cancer disorders, for example, Lynch syndrome, Petuz Jeghers syndrome, familial adenomatous polyposis and familial atypical multiple mole melanoma syndrome. All of these are represented by germ-line mutations and related with expanded risks of pancreatic malignancy. The second group involves the hereditary pancreatitis and cystic fibrosis conditions with an inherited inclination to the advancement of pancreatic cancer. The third group indicates familial pancreatic cancer that does not satisfy the criteria of other genetic cancer disorders with expanded risks of pancreatic cancer. (Lin., Yang,Jin,& Fu, 2015)

Cancer in children: The sorts of cancer that occur in children are frequently different from the cancers that occur in adults. Childhood cancers are the consequence of DNA changes in cells that may occur before birth while adult cancers are caused by lifestyle or environmental risk factors; the reason for childhood cancers is not always known. It is predicted that around 5% of all cancers in children occur from genetic (inherited) mutation that can be transferred from parents to their kids. For instance, 25-30% of eye cancers in children called retinoblastoma are caused by defects in gene RB1which is an inherited mutation. In any case, retinoblastoma represents just around 3 % of all cancer in children. However, Fanconi anemia syndrome, Noona syndrome, Beckwith-Wiedemann syndrome ,

Li-Fraumeni syndrome and Von-Hippel syndromeare called familial syndrome which showed inherited mutation and increase the risk of childhood cancer.

Genetic mutations can happen amid the development of fetus in the womb. For instance, one in every 100 children is conceived with a hereditary mutation that increases risk for leukemia. However, only one child in 8000 with that mutation ultimately develops leukemia (National Cancer Institute, 2014). Children with Down syndrome have an extra chromosome of 21 which are referred to create malignancies for example leukemia and testicular cancer, however the purpose behind this is not surely known. (Ross, Spector, Robison & Olshan, 2005).

2.1.1 Genetic makeup

The genotype refers to the DNA sequence of an individual as often referred to the hereditary code and passed from one generation to another.

Kaposi sarcoma (KS) is a rare type of cancer that occurs in the line of lymph or blood vessels. It mainly affects the skin or mucosal surface such as inside the mouth, however it can occur in any part of the body like in the lymph nodes, the lungs, or digestive tract. There are different types of KS which develop in different regions. For example, epidemic or AIDS related KS is most common in the United States. People who are infected with HIV virus that may cause AIDS are prone to this type of KS. On the other hand, classic KS develops mostly in older people of the Mediterranean, Eastern European, and Middle Eastern heritage. Men are more susceptible to classic KS than women. People tend to have one or more lesions on the legs, ankles, or the soles of the feet. The lesions do not grow as quickly as other types of KS and it takes time to develop new lesions. There is another type of endemic (African) KS which mostly develops in the people of Equatorial Africa and is named after African KS. It is most common in younger people under the age of 40. The infection called KSHV (Kaposi sarcoma associated herpes virus) is more common in African people than people from other parts of the world. In African people AIDS is the most common type of disease, so endemic type is believed to be more common in Africa. (American Cancer Society, 2016)

Thus genetic makeup plays an important factor in increasing one's risk to develop cancer. Scientists are identifying a number of hereditary disorders which may bring about disease and illness in their carriers. The mapping of the human genome makes analysis more precise and medications more successful.

2.2 Environmental factors

Cancer in Oral Cavity and Pharynx

Mouth: The main risk factors for most mouth cancer are tobacco and alcohol uses. Diet low in fruits, vegetables, ingestion of food and drinks at high temperature can also develop the risk for these cancers (Key. et al., 2004; Shridhar. et al., 2016). Apart from that certain types of HPV (Human papillomavirus) infections can also be a risk factor for oral cavity cancer, though their accurate prevalence and clinical significance still not clear. Use of mouthwashes with high-alcohol content, iron deficiency anemia, poor oral hygiene and hypodontia or anodontia could be possible risk factors for mouth cancer. Chewing betel leaf, oral snuff and betel quid substituent which are locally called as khaini, mawa, mishri, gudakhu, nass,naswar and guktha, sweetened dry mixture of areca nut ,catechu ,using all these substances have a higher risk for developing mouth cancer. (Lee et al., 2015; Sankaranarayanan, Ramadas, Amarasinghe, Subramanian, & Johnson, 2015).

Cancer in Digestive system

Colorectal cancer: Apart from the familial or hereditary risk factors, there are some diet-related risk factors behind the development of colorectal cancer. Obesity/over weight is the major risk factor for this cancer. Alcohol shows a relatively less increase risk but it cannot be neglected. Physical inactivity, diet low in fiber, vegetables is also important risk factors (Key. et al., 2004). Furthermore, consumed 30g of red and processed meat per day increases the risk by 10% for colorectal cancer. There are some limited studies showed the link of animal fats to the risk of colorectal cancer. Nevertheless, high level of secondary bile acid in the lumen of the large intestine because of high intake of fat may increase the risk of intestinal inflammation and other diseases. Tobacco smoking represents 12% of colorectal

cancer cases and double the risks for colorectal cancer. (Raskov.,Pommergaard., Burcharth., & Rosenberg., 2014).

Pancreatic cancer: Use of tobacco is one of the main risk factors for many cancers and also for pancreatic cancer. It accounts for 9% of cancer deaths to male smokers and male smokers have 74% of higher risk of pancreatic cancer. Obesity/overweight and some dietary factors also increase the risk of pancreatic cancer. Other than that diabetes mellitus thought to be a risk factor though the result is still ambiguous. Some of the studies have shown a relationship between pancreatic cancer and diabetes mellitus where 25% of patients diagnosed with pancreatic cancer had diabetes mellitus and among them 40% were pre-diabetic. Moreover, chronic pancreatitis, allergies, diet high in meat or butter fat, alcohol and coffee or tea consumption are other possible risk factors for pancreatic cancer. (Lin. et al., 2015).

Stomach cancer: Helicobacter pylori, indeed, is one of the main risk factors for stomach or gastric cancer. Dietary nitrates which can be found naturally in foods such as cauliflower, celery, radish beets, carrot, cabbage and spinach and they can be added in the food during preservation. One study surveyed that dietary nitrate transformed into carcinogenic N-nitroso compounds by gastric acid and increases the risk of stomach cancer. Furthermore, high intake of salted, pickled or smoked foods, dried fish, meat and carbohydrates notably develop the risk for stomach cancer. Then, alcohol consumption, cigarette smoking, high dose of ionizing radiation and genetic factors are important risk factors for stomach cancer (Compare, Rocco, &Nardone, 2010; Saghier, Kabanja, Afreen, &Sagar, 2013).

Liver Cancer: Infection with hepatitis B or C virus is the main risk factors for liver cancer. Aflatoxins, which are found in improperly stored staple items like peanut, rice, corn, seed etc. are the major risk factor for liver cancer. Obesity /overweight have a significant contribution to the risk of liver cancer. Among the diet-related risk factors, excessive alcohol consumption is a pre-dominant one. Occupational exposure to vinyl chloride monomer (VCM), polyvinyl chloride (PVC) organic solvents, thorium dioxide or vinyl chloride, chlorinated pesticides and arsenic can adversely affect the liver and can cause cancer. Other risk factors are some inherited metabolic diseases (e.g. hemochromatosis), use of steroids,

smoking and Wilson's disease. (Janevska.,Chaloska-Ivanova., &Janevski., 2015; Key. et al., 2004; Rapisarda et al., 2016).

Esophageal cancer: Excessive alcohol consumption and tobacco smoking like cigarettes, cigars and pipes are the major risk factors for esophageal cancer. Poor diet, obesity, folate deficiency, decreased level of certain nutrients (thiamine, zinc, riboflavin, carotene, and ascorbic acid), inadequate ingestion of fruits and vegetables and high level of sodium chloride and animal fats are possible risk factors for this cancer. (Key. et al., 2004; Peng., Chen, &Huo., 2016; Szumilo, 2009).

Gall bladder cancer: The major risk factor is formation of gallstones for gallbladder cancer. In case of female the risk factors are early marriage and the number of child births. Other possible risk factors which are turned out to be important are ingestion of oily/fried food, exposure to wood and coal dust, long interval between meals, use of tobacco and use of estrogen-containing drugs (Jain,Sreenivas,Velpandian,kapil,&Garg, 2012).

Cancer in Respiratory System

Lung cancer: Nearly 80-90% of all lung cancers are responsible for tobacco using. Passive smoking is also important contributory risk factors for lung cancer. Occupational exposure to radon and various other gases such as vinyl chloride, asbestos, chloromethylethers or by products of fossil fuel and high doses of ionizing radiation are also thought to increase the risk of developing lung cancer. Exposure to air pollution including the emission made out of polycyclic aromatic hydrocarbon which is considered a distinguishable risk factor for lung cancer and has been connected with an 8% expanded risk of all cause lung cancer mortality. Insufficient ingestion of fruits and vegetables have been also connected with lung cancer (Choi, Park, Noh, Kho, &Kang., 2016; Key. et al., 2004; Zappa. &Mousa., 2016) .

Skin Cancer

Melanoma: Severe sun burn, fair skin, multiple moles or atypical moles (colored skin spots), personal or family history of melanoma and excessive exposure to ultraviolet radiation are the main risk factors for melanoma cancer. Melanomas are mostly seen among white peoples. (Lo & Fisher, 2014).

Non-melanoma: Long time exposure to ultraviolet radiation (sun light), fair skin, high doses of ionizing radiation and rare hereditary diseases such as multiple basal cell carcinoma syndrome, xerodermapigmentosum and albinism are main risk factors for non-melanoma cancer. Possible risk factors are chronic infections, poorly made cosmetics, photo sensitizers in tanning aids, burn scars and reduced immune function due to organ transplants or viral infection. (Preston & Stern, 1992)

Breast cancer: For female breast cancer the identified risk factors are personal history of ovarian or endometrial cancer, family history, early menarche, infertility, and late pregnancy after age 30, high dose of ionizing radiation, long term use of post-menopause estrogens and progestin, post-menopausal obesity and excessive alcohol consumption. (Key. et al., 2004; Weir, Day, & Ali, 2007). For male, the risk factors are family history, aging, expose to radiation, Klinefelter syndrome, testicular disorders. Possible risk factors include gynesomastia and obesity. (Hsing., McLaughlin., Cocco., Chien., & Jr., 1998)

Cancer in Reproductive Organs

Prostate cancer: Family history especially father or brother and race/ethnicity are main risk factors for this cancer. Prostate cancer occurs more in black male than white male. Obesity, high intake of animal fat, sexually transmitted agent, smoking, alcohol, hormonal factors and lack of physical activity are possible risk factors for prostate cancer. The known risk factors are infertility, overweight, hypertension, diabetes and Stein-Leventhal syndrome. (Gann, 2002;Key.et al., 2004)

Ovary cancer: Family history of breast or ovarian cancer, personal history, and susceptibility genes (BRCA-1, BRCA-2) are risk factors for ovarian cancer. Ovaries exposed to the pelvic contaminants and carcinogens can be the etiology behind the ovarian cancer. Possible risk factors are high consumption of fat, dairy product and dietary fat. Additional risk factors include nulliparity and refractory infertility.(Holschneider & Berek, 2000; Key. et al., 2004)

Cervix cancer: Long term use of oral contraceptive use, early sexual intercourse, many sexual partners, HPV infection, multiple birth and cigarette smoking are the risk factors for cervix cancer. (Key. et al., 2004; Natphopsuk. et al., 2012).

Cancer in Urinary System

Bladder cancer: Smoking is one of the important risk factors for bladder cancer. Occupation in the dye, leather or rubber industry, occupational exposure to aromatic amines and PAH (polycyclic aromatic hydrocarbons) increase the risk of bladder cancer. Possible risk factors are arsenic contaminating water, urinary tract infections, heavy coffee consumption, long term use of pain killers containing phenacetin and genetic factors (Jankovi´c. &Radosavljevi´c., 2007).

Kidney: The most important risk factor is smoking. Apart from that, obesity, exposure to arsenic, abuse of analgesic (especially phenacetin-containing pain killers) is also contributor to kidney cancer. High meat consumption and use of prescription diuretics are possible risk factors for kidney cancer. (Chow, Dong, & Devesa, 2010).

2.2.1 Epigenetic changes

Epigenetic factors may be defined as a change in the gene expression without affecting the change in the DNA sequence. Epigenetic changes might be indirectly including many environmental factors like the presence of pathogens, parasites, unsafe chemicals and anxiety levels.

There is an expanding proof that transcriptional reprogramming brought about by epigenetic modification can be transferred from parents to their offspring. Without a doubt, for example, cancer in the offspring can be caused because of epigenetically gene expression profiles prompted by anxiety experienced by the parent. Insects models have been utilized for human disease with epigenetic component because the underlying molecular mechanism (DNA methylation, expression of micro RNAs and histone acetylation) are developmentally conserved. (Mukherjee, Twyman,& Vilcinskas, 2015)

Epigenetic gene regulation contains nucleosome which is on the focus stage. The nucleosome is comprised of around two turns of DNA enclosed around a histone octamer manufactured from two subunits of every histone H2A, H2B, H3 and H4, individually. The linker histone H1 in the midst of the center nucleosome connects and promoting compaction. The N-terminal tails of the histone proteins are jutting out from the nucleosomal centre particles and further these tails performs as a base to which epigenetic changes to be composed (Lund & Lohuizen., 2004). Methylation happens in the mammalian genome at cytosine bases found in 5' to a guanosine in a CpG dinucleotide. Many of the CpG islands are presented in the proximal promoter locales of half of the qualities in the mammalian genome that are unmethaylated in somatic cells.

Therefore, the hypermethylation of these promoter regions in cancer is considered as the most well designated epigenetic changes happened in tumors. Practically, in every human neoplasm this change has noticed and linked with the improper transcriptional silencing of genes. About half of the gene that bring familial cancer and are seen to pass through methylation related silencing in different sporadic types of cancers. BRCA1 studies in the etiology of non-familial cancer states the significance of epigenetic silencing. Although this gene was responsible for only familial breast cancer by BRCA1 germ-line mutation, around

10-15% of women with the non-familial breast cancer have noticed to have the BRCA1 gene hypermethylated. (Jones, & Baylin, 2002).

Epigenetic modifications, for example CpG island DNA methylation are included in gastric cancer (GC) and promoter methylation is thought to be one of the key procedures required in inactivate tumor suppressor gene. GC progression has been connected with epigenetic inactivation of various genes. Nonetheless, it incorporates genes required in cell cycle control (CDKN2A), DNA repair (MLHI), cell adhesion/attack/movement (CDH1), transcriptional control (RUNX3) and numerous others. The RUNX3 transcription factor has been identified as poor tumor suppressor gene and has been connected with early inflammatory, pre-neoplastic tumor stages and in addition with chronic H.pylori infection which can lead to inflammation in gastric tissue and henceforth quicken the inflammation related cancer development (Llorca-Cardenosa et al., 2016).

Penile carcinoma (PeCa) is a vital public health issue in poor and developing countries. Human Papillomavirus has been considered as important risk factors for malignant penile lesions. Others are phimosis, poor genital hygiene, tobacco uses. Apart from its unpredictable behavior and forceful treatment, there have just been a couple of reports with the respect to its molecular data particularly epigenetic mechanism. Epigenetic changes for instance, CpG islands methylation, may uncover possibility for the change of specific markers for malignancy discovery, analysis and prognosis. However, couple of reports that shows the epigenetic alteration in PeCa and these studies has just centered on alteration in particular genes in a predetermined number of cases. A greater amount of studies depicting epigenetic changes of PeCa the majority of which assessed the methylation of CpG islands specific genes. Among them six studies explored the CpG island status of CDKN2A. Two tumor suppressor proteins such as p16INK4A and p14ARF are encoded by CDNK2A which control cell development through the Rb-CDK4 and p53 pathways. On the other hand tumor suppressor gene CDKN2A obstructs the cyclin-subordinate kinases 4 and 6, which are included in the initiation of cell cycle and the hindrance of CDK-mediated phosphorylation of the RB gene. Besides, the epigenetically mediated loss of CDKN2A is a standout amongst the most widely recognized and earliest events in human carcinomas. (Kuasne, Marchi, Rogatto, & de SyllosColus, 2013).

2.2.2 Interaction with immune system

The consequences of the most recent research showed the relationship between chronic inflammation and cancer. Inflammatory process makes microenvironment for the development of neoplasm. Malignant process begins to develop, when the chronic inflammation or recovery of tissue takes place. Inflammatory cells not just make appropriate microenvironment for improvement of neoplasm, additionally discharge number of cytokines and growth factors advancing survival of a neoplasmatic cell and inhibiting apoptosis. The host anti-tumor activity is controlled between carcinogenesis and in this way tumor-promoting immune activity aids tumor growth, angiogenesis, invasion and metastasis.

The process of inflammation promoting tumor growth and suppression of anti-tumor immunity by cancerous cell has been remaining a huge challenge. As of late, hereditary knockout mice models and biochemical studies have uncovered that two transcription factors, NF-kB and STAT3, are main considerations connecting inflammation to cancer. Chronic infections and inflammation are thought to be important risk factors for many types of cancer. In addition, cytokines and other pro- inflammatory factors modulate expression of genes important in carcinogenesis; they likewise initiate NFκB and STAT3 dependent signaling pathways which support neoplasmatic cells to keep away from apoptosis. Until their role in colon, gastric and liver cancer have been widely researched (Fan, Mao,&Yang, 2013; Francuz, Czajka-Francuz, Cison-Jurek, &Wojnar, 2016).

The role of immune system in skin cancer has been explained by the increased incidence of skin cancer in organ transplant recipients (OTR). OTRs are at increased risk of developing non- melanoma skin cancer. Patient with organ transplant take immunosuppressive drugs which make them more susceptible to develop cancer. Immunosuppressant, viral infection and impaired DNA repair and p53 signaling all interact in OTRs to create extreme risk for non-melanoma skin cancer (Wheless, Jacks, Mooneyham Potter, Leach, & Cook, 2014).

There are few sorts of inflammation for example gastric cancer is connected with ***Helicobacter pylori*** infection. Then hepatocellular carcinoma can be characterized by infection with hepatitis B (HBV) or C (HCV) viruses and infections with ***Schistosoma*** or ***Bacteroides*** species are connected to bladder and colon cancer, individually. As an after

effect of these distinctive types of inflammation, there are some innate immune cells present in the tumor microenvironment (counting neutrophills, mast cells, myeloid derives suppressor cells, macrophages, dendritic cells and natural killer cells) and adaptive immune cells (T and B lymphocytes) around the cancer cells and their surrounding stroma (which comprises endothelial cells, pericytes, fibroblasts and mesenchymal cells). Production of cytokine and chemokine aids in the communication of these different cells and function in a paracrine and autocrine system to restraint and determine tumor growth. Tumor associated macrophages (TAMs) and T cells are immune cells, which are found in the tumor microenvironment mainly aid in the tumor growth and high TAMs normally show the poor prognosis of the disease.

Despite of the source, the distinctive cytokines can either advance or hinder the development of tumor. Activation of different downstream effectors, for instance, NF-kB, STAT3, cytokines monitor the immune and inflammatory environment to either support anti-tumor immunity or improve tumor movement .Furthermore, this effectors have immediate effect on cancer cell growth or survival. Carcinogenesis is also influenced by other immune cells. Neutrophils can either promote tumor growth or act as tumoricidal, mainly depending upon their separation status and the existence of TGF-β (transforming growth factor beta). Mast cell and B lymphocytes are the contributors of immune-mediated tumor growth. (Grivennikov, Greten, & Karin, 2010).

2.3 Cancer type specificity

Table 3.1: cancer type specificity associated with specific risk factors

Cancer type	Risk factors
Lung cancer	Tobacco smoking Exposure to radon Asbestos and other substances Air pollution
Colorectal cancer	Obesity Alcohol consumption Tobacco smoking Diet high in red meat
Pancreatic cancer	Tobacco Diabetes Chronic pancreatitis
Stomach cancer	Infection with ***Helicobacter pylori*** High intake of salted, pickled or smoked foods
Liver cancer	Hepatitis B or C virus Obesity
Esophageal cancer	Tobacco smoking Alcohol consumption Barrett's esophagus
Gallbladder cancer	Gallstone Exposure to environmental chemicals Female gender Fried food
Prostate cancer	Race/ethnicity Obesity High intake of meat
Ovarian cancer	Infertility
Breast cancer	Obesity Radiation
Oral cavity	Chewing betel leaf and betel quid substituents Tobacco smoking

Bladder	Tobacco smoking Occupational exposure to chemicals Long term use of pain killers
Kidney cancer	Tobacco smoking High meat consumption Obesity
Skin cancer	Fair skin Severe sun burn UV radiation

2.4 Regional Variation

Table 3.2: variation in the cancer prevalence of different region

Region	Cancer Both sexes(male and female)		
	Incidence	Mortality	5 years prevalence
	Estimated number (thousand)		
More developed region	6054	2873	16823
Less developed region	8014	5323	15632
United States of America	1604	617	4775

India	1015	683	1790
China	3065	2206	5045
Japan	703.9	378.6	2008.5
Bangladesh	122.7	91.3	251.8

Source: GLOBOCAN 2012

Chapter 3

Evaluation of current methods for identifying cancer risk factors

There are some tests or programs which are assigned to find out whether a chemical or bacteria or any lifestyle, genetic or diet-related factors contributes to the development or progression of carcinogen. In the following, some test or programs are explained which are being used or invented by the scientists to determine the risk factors for cancer.

3.1 Cohort study

Cohort studies are type of observational study which is used to examine the etiology of disease, building the relationship between risk factors and its outcomes. Cohort studies begin with a result or with a group of people free of disease by looking into the exposure or occasion of interest and the study is continued until the desire disease or outcome happens. Since exposure is distinguished before the result, these studies have a transient system to evaluate incidence and in this way can possibly give the most grounded logical confirmation. Rare exposures can be examined since subjects are chosen by their exposure status which is an advantage of this study. Apart from that, the examinees can analyze numerous results all the while. It requires large samples and long periods of follow up plan causes more expenses which are disadvantages of this study.

Cohort studies are of prospective and retrospective type. In the prospective studies, the study is conducted from present time into what's to come. Since prospective studies are outlined with particular information accumulation techniques, it has the benefit of being customized to gather particular exposure information and in this was it might be more complete. In this study the follow-up period is to long too seat up tight for any occasions or disease to happen and it indicates the weakness of this study.

A retrospective study which is likewise known as historical cohort studies, are done right now and look to the past to analyze any outcomes or medical events. Here, the subjects of cohort are chosen presently in the light of exposure status and result data such as disease status, occasion status, which was counted previously, are reproduced for evaluation. The weakness of this study is the constrained control over data collection. The current information might be inadequate, wrong or conflictingly measured between subjects. However, due to the prompt accessibility of the information, the outline of this study is inexpensive and concise than the prospective studies.

3.2 Case –control study

In case-control studies, by analyzing the result status the subjects are identified at the beginning of the examination. The outcome of interest where the subjects might have experienced a particular sort of surgery, encountered a complexity, or is determined to have a disease. At the point when result status is perceived and subjects are arranged as cases, controls (subjects without the outcome however from the same source populace) are picked. Data about introduction to a risk factor or variable risk factors is retrospectively assembled commonly by taking interview, deliberation from review and/or records, survey.

As subjects are chosen from their result status at the beginning, case-control studies are appropriate to explore uncommon disease or rare disease with a prolong inertness period. (Song & Chung, 2010).

3.3 In vitro-In vivo studies

Hypothesis about cancer development, progression and risk factor are difficult to test directly in a patient population. In vitro-In vivo studies are broadly used to concentrate on the etiology of cancer and to look at the components affecting the factors of tumors progression.

In vitro study

Here, the tumor cell lines are used that are transplantable rat tumors and can be modified or decided for development in cell culture. In vitro, the cells are usually grow and clone. Standard cell culture techniques are utilized to study the cell lines. Animals are being injected with the cell to form tumors which can be processed and contemplated utilizing standard end points for tumor reaction. Exactly when tumor cells are plated in agar or on petri dishes, colonies are made with high plating proficiency. This allows the survival (clonogenecity) of tumor cells treated in vivo to be analyzed in vitro. (Rockwell, 1980).

In vivo study

In vivo test research became widespread with the utilization of microorganism and animal models in hereditary control tests and the utilization of animal models to examine the drug toxicity, harmful chemical, mutagens etc. Researcher have utilized prokaryotic, unicellular

eukaryotes like yeast and also utilized mice model to study genetics, molecular biology and toxicology. The activity of gene can be studied by either watching the impacts of spontaneous mutation in whole organism or by presenting focused mutation in cultured cells. It is feasible to construct particular mutation in whole animals because of the introduction of gene cloning and in vitro mutagenesis hence impressively encouraging in vivo research. Mice with additional duplicates or modified duplicates of a gene in their genome can be produced by transgenesis, which is currently an entrenched system. Moreover, the capacity of a specific gene can be completely seen just if a mutant animal who does not express the gene can be acquired. (Lodish. et al., 2000)

This is currently accomplished by gene knock-out technology where the gene of interest first segregate and after that supplanting it in vivo with a defective duplicate. This model is called mouse gene knockouts. There are other various mouse model used in the in vivo to study the loss of gene function such as mouse conditional gene mutations, mouse model of RNA interference, mouse single-cell knockouts. (Walrath, Hawes, Van Dyke, & Reilly, 2010)

In vitro and In vivo studies are useful model to anatomize and analyze different factors which can contribute to cancer development. In any case, they are different artificial models which have biological characteristics different from those of human cancer. The biological characteristics should be fundamentally taken into consideration when the frame works are utilized to consider the etiology or treatment of cancer, to guarantee that the tumors are suitable and legitimate models for the issues being analyzed. (Rockwell, 1980).

3.4 Ames test

The test was first established in 1970 by Bruce Ames and his group at the University of California, Berkeley. This test is used to determine whether a chemical is mutagenic or not. The Ames test is based on that assumption that any substance which is thought to be mutagenic for the bacteria used in this test may emerge as carcinogen and can cause cancer. ***Salmonella typhimurium*** bacteria strain with a mutation in gene is used in this test which is lack of amino acid histidine (His) from the ingredients in its culture medium. Nonetheless, some of the mutation incorporating this one can be reversed that is called back mutation

with the capacity of recovering gene function. These bacteria can develop on a medium which lack in histidine.

Not all chemicals are mutagenic or cancer causing substance, but rather get to be changed over in to mutagen when they are metabolized by the liver. This is the etiology behind using the mixture of rat or hamster liver enzyme (S9) in the Ames test to observe the metabolic conversion of the test chemical. It actually helps the investigator to determine if a chemical need to be metabolized to express mutagenic activity. Since some mutagenic chemicals are active with and without metabolism, while others are active only under one condition or the other. A few measurements (not less than 5) of every test chemicals and different strains of microscopic organism are utilized as a part of every trial. Thus, cultures are made with or without included liver S9 enzymes at different concentrations. Therefore, various culture conditions are employed to boost the chance to distinguish a mutagenic chemical. Repetitive tests are done to check all observed responses. If there is no event of increase mutant colonies after several strains under several different conditions, the test is then thought to be non mutagenic in the Ames test. The limitation of this test is that ***Salmonella typhimurium*** is a prokaryote and thus not a perfect model of the human body. For this reason, liver enzymes are added to the test to mimic the mammalian metabolic condition. Human and rat have different metabolism which can influence the mutagenicity of the chemicals being tested. The test may in this manner be enhanced by the utilization of human liver S9, although its utilization was already limited by its accessibility, yet it is presently accessible commercially and in this way might be more possible. Another rapid in vitro tests model on the Ames test have been adapted for some eukaryotic cells for example yeast. (Mortelmans & Zeiger, 2000; "The Salmonella/E. coli Mutagenicity Test or Ames Test," 2016).

3.5 NTP (National Toxicology Program)

NTP was established by Joseph A. Califano, Jr, Secretary of Health, Education and Welfare in 1978 and run by the United Department of Health and Human services to coordinate, evaluate and report on toxicology within public agencies. In the United States, more than 80000 chemicals are being registered and expected 2,000 new chemicals are presented for use in everyday items such as in foods, personal care items, doctor prescribed drugs etc. We do not have a clue about the effects of these chemicals or products on our health and some

of them might be a significant risk to human health. To understand the toxicology of these chemicals in our body, NTP program is conducted and the program was created with an agreeable attempt to:

- Organize toxicology programs inside the federal government
- Reinforce the science base in the toxicology
- Develop and approve enhanced techniques
- Provide data about conceivably toxic chemicals to health, research agencies and, regulatory, scientific and medical communication and the public. (Birnbaum. & Bucher, 2016).

3.6 Gaps in knowledge

Cancer researchers have identified certain risk factors of developing cancer through epidemiological studies. Scientists use several methods, tests and programs to find out the toxic substance which can cause cancer. Some of the studies, on their own cannot prove that a behavior or substance causes cancer e.g. a particular substance that can be a true factor other than the suspected risk factors. This type of information can move the ideas in a wrong way about the cancer causes and associated risk factors.

It is sometimes difficult to keep in pace with the new invention of various synthetic materials which are being used in cooking, food industry and in clothing industry. These synthetic materials can be suspected risk factors for cancer development. As the suspected risk factors are increasing due to new invention of various elements in the environment, it is not always feasible to carry out experiment regarding its association to the cancer development.

The mechanisms for epigenetic changes have not yet established for majority of cancers. In spite of the fact that the screening of foods and individual chemicals done by Ames assay for nucleotide mutagen, the screening for clastogens has been found to be inefficient (Hossain et al., 2013).

Increasing information create gaps between various socioeconomic status (SES) groups as higher SES groups will probably obtain this new data at a faster rate than lower SES groups. Therefore, these gaps make disparities in health and different risk factors between various social groups.

Most of the tests in developed countries are performed mostly on the white population, so there is a lack of data about non-white and other various ethnic groups. Thus, most of the tests are carried out in developed countries; they might found some unique risk factors which can be the true risk factors for other developing countries as well. The people of developed countries are more aware about the causes of cancers than the less developed countries and may allow them to protect themselves and minimize their risks (Viswanath et al., 2006).

Many ethnic groups are not aware about the causes and risk factors of cancer which is why the incidence and death rates are higher among them as they lack access to medical coverage, not privileged to early detection and screening and due to absence of access to proper cancer treatment.

However, in some studies models are used to examine any factors which can lead to cancer development. The biological characteristics of artificial models are sometimes different from the human cancer (Rockwell, 1980).

3.7 Proposed studies

Cancer incidence and mortality rates are increasing day by day. Environmental risk factors play a vital role in the etiology of cancer. It is not always possible to keep our self-protect from those risk factors. All the environmental risk factors cannot be avoidable but those such as tobacco smoking, alcohol consumption etc. which responsible for majority of the cancer. Heavier media coverage showing the effect of those products on health could help to some extent.

Furthermore, the use of natural product should be increased because natural products are better than the synthetic materials to which people are getting habituated because of the evolution. Synthetic materials can pose some chemicals which can cause changes in our genome, thereby, resulting in cancer. People should be cautious in using synthetic material.

In a study researcher found some potent DNA damaging characteristic in some dietary agents (coffee, tea, liquid smoke) by using the p53R assay. The p53R assay is sensitive to DNA strand breaks. Therefore, p53R assay can be used for screening clastogen in further studies to find out any agents which can be DNA strand breaker and cause carcinogen or other disease (Hossain, Patel, & Kern, 2014).

Conventionally, scientific research has concentrated on examining singular occasions, for example single mutations on gene function. A scope of advancements is starting to give data that will empower a comprehensive perspective of how genomic and epigenetic variations in cancer cells can modify the homeostasis inside these cells, between tumor cells and the

nearby microenvironment and also at the organ and organism level. This procedure is called system biology which is coordinated with a frequent process where the speculations and expectations that emerge from modeling are refined and compelled by exploratory evaluation. System biology plays a crucial role for creating and executing powerful techniques to convey customized malignancy treatment (Werner, Mills, & Ram, 2014).

More test or method should be established in accordance with the new invention of materials or elements in food, cloth industry. A larger registry should be maintained of cancer patients to find out any important trends or fact that could possibly affect the patients. The better study design and tools are needed to conduct population-based study for better understanding of their environment, dietary habits etc. Epidemiological studies should be done more on non-white population and other various ethnic groups. Moreover, adequate test should be done for the risk factors which are new to the developing world.

Technology is as of now assuming a noteworthy part in lot of the research and its effect will probably develop in future. For instance, there are now many apps on mobile phone which can keep track of dietary data and can be utilized to fortify endeavors to stop smoking.

Online networking platforms can be utilized to disperse data about cancer control or any suspected factors customized to particular population and to gather information on how this data influences health related behaviors.

Chapter 4

Conclusion

Conclusion

In the current situation, cancer incidence is increasing day by day. Different risk factors (age, sex, genetic, environmental, occupation etc.) contribute to cancer development. The type of cancers that are most prevalent include stomach cancer, blood cancer, esophageal cancer, breast cancer etc. which have been found to be often associated with exposure to various environmental and dietary factors. People should be more conscious about their surroundings and the products they use. As the population increases worldwide, changes happen in the society, family structure, occupation; people are more susceptible to be exposed to the various factors which make them more vulnerable to those risk factors. Avoiding tobacco chewing, smoking and alcohol consumption may be some of the feasible preventive measures to avoid developing cancer. At early stage, treatment of cancer is one of the best ways to stop spread of cancer. As well as by leading a healthy life style, we can minimize our exposure to certain risk factors and might lower our risk to develop cancer. In future there should be research done among the all classes of cancer patients from diverse ethnic groups, so that identification of these factors will be more meaningful and give more generalizable conclusions.

Chapter 5

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