A review on dangerous neoplasm cancer

Vipin Kesharwani, Sudha Kumari, Nikhil Kushwaha and Kuldeep Singh

Abstract
Cancer in the broader sense refers to more than 277 different types of cancer disease. Scientists have identified the different stage of cancers, indicating that several gene mutations are involved in cancer pathogenesis. These gene mutations lead to abnormal cell proliferation. A genetic disorder caused by heritance or inherittance factor has a pivotal role in the increase of cell growth. The in the 1980s groundbreaking evidence began to emerge that a variety of viruses also cause cancer in human. There is now sufficient evidence of carcinogenicity in human T-cell lymphotropic virus, human immunodeficiency virus, hepatitis B virus, hepatitis C virus, human papillomavirus, Epstein-Barr virus, and human herpes virus 8 according to the International Agency for research on cancer (IARC). With the assistance of technological advances in bioinformatics and molecular technique, additional information has been obtained that can be useful for early diagnosis and proper treatment. These can also be complemented with enzyme supplement. Understanding the molecules basis of cancer can give us an insight into the protocol for aggregate prevention, treatment, oral and curing of cancer.

Keywords: Gene mutation, IARC, molecular basis, carcinogenicity

1. Introduction
Cancer is the second leading cause of mortality worldwide. Overall, the prevalence of cancer has actually increased; just in the United States alone, approximately 1,665,540 people suffered from cancer, and 585,720 of them died due to this disease by 2014 [1]. Therefore, cancer is a serious problem affecting the health of all human societies. Unfortunately, it is a variety of disease at the tissue level and this variety is a major challenge for its specific diagnosis, followed by the efficacy of treatment [2, 3]. Nutrition is the science that deals with the composition and chemical properties of food and how the body uses the nutrients in one’s diet [4]. In men, the highest percentages of cancer types occur in the prostate, lung and bronchus, colon and rectum, and urinary bladder, respectively. In women, cancer prevalence is highest in the breast, lung and bronchus, colon and Rectum, uterine corpus and thyroid, respectively. This data indicates that prostate and breast cancer constitutes a major portion of cancer in men and women, respectively [5]. In 1950, the World Health Organization sponsored an international symposium, and the attendees were intrigued by the dramatic Variations in the types of cancer found in different areas of the world [5]. The symposium led to the Creation of the International Agency for Research on Cancer (IARC) in 1965 which was instructed to conduct multidisciplinary investigations of the causes of human cancers [6, 7]. The assessments of the IARC were initially based only on epidemiological evidence [7], and then later the criteria were extended to include experimental evidence [8]. In 1973, nutrition was defined as the science that deals with the composition and chemical properties of food and how the body uses the nutrients in one’s diet [9]. Diet may increase or decrease the risk of certain cancers [10]. A suggestion from the examination of the associations between dietary patterns and cancer rates in different populations around the world [12] and thus revealed, according to [13] that 30-40 per-cents of cancer cases are preventable by appropriate dietary means. In line with this, some specific foods, herbs, and spices have been discovered to be potent anti-cancers [14] while some others are contributing factors to cancer risk [15]. Cancer treatments are delicate and expensive; chemotherapy and radiation are not specific as they destroy normal (host), as well as, cancer cells. They don’t cure cancer but slow its growth [16]. It is on this premise; this review reports some unhealthy foods to be avoided and those important super foods to be encouraged in order to prevent cancer development and thus indicating the saying that prevention is better than cure. Viruses, bacteria, and radiation rays are other carcinogenesis factors, comprising about 7% of all cancers [17]. Normally, repair genes translate to protein and enzymes that have repairing properties and more than 30 types of detected repair proteins [18].
Removing uracil from DNA bypasses the DNA damage and removes the main DNA lesions induced by ultraviolet light, which are essentially the functions of repair genes to successfully repair DNA [19]. Epigenetics is a dynamic situation during the study of cell fate and epigenetic modifications such as DNA methylation, histone modifications and nucleosome position, which play important roles in cancer formation [20, 21]. Cancer cells are characterized by a vast reduction in DNA methylation (about 56% reduction in the total amount of 5-methyl cytosine) [22]. Overall reduction of mono acetylated H4K16 forms the majority of histone modifications in cancer cells [23]. All families of chromatin-modifying proteins are associated with cancer, although in most cases, the molecular mechanisms underlying their functions remain unknown [24]. In this study, we reviewed cancer of neoplasm of the level in order to get closer their look at this disease.

2. History of Cancer
Cancer is the second leading cause of death in the world after cardiovascular diseases. Half of the men and one-third of women in the United States will develop cancer during their lifetimes. Today, millions of cancer people extend their life due to early identification and treatment [25]. Cancer is not a new disease and has afflicted people throughout the world. The word cancer came from Greek words Karakinos to describe carcinoma tumors by a physician Hippocrates (460-370 B.C.), but he was not the first to discover this disease. Some of the earliest evidence of human bone cancer was found in mummies in ancient Egypt and in ancient manuscripts dates about 1600 B.C. The world’s oldest recorded case of breast cancer hails from ancient Egypt in 1500 BC and it was recorded that there was no treatment for cancer, only palliative treatment. According to inscriptions, surface tumors were surgically removed in a similar manner as they are removed today [27].

3. Old Theories about Cancer [28].
3.1 Humeral theory
Hippocrates believed that the body contained 4 senses of humor (body fluids), (a) blood, (b) phlegm, (c) yellow bile and (d) black bile. Any imbalance of these fluids will result in disease and excess of black bile in a particular organ site was thought to cause cancer. This theory of cancer was standard through the Middle Ages for over 1300 years. During this period autopsies were prohibited for religious reasons, thus limiting knowledge about cancer.

3.2 Lymph theory
This theory proposed that cancer formation was by fluid called lymph. Life was believed to consist of continuous movement of the fluids like blood and lymph in the body. The lymph theory was supported in the 17th century that tumors grow from lymph constantly thrown out by the blood.

3.3 Blastema theory
Muller demonstrated that cancer is made up of cells but not with lymph in 1838. His student, Virchow (1821-1902) determined that all cells including cancer cells were derived from other cells.

3.4 Chronic irritation theory
Virchow proposed that chronic irritation was the cause of cancer. Later Thiersch was showed that cancers metastasize through the spread of malignant cells and not through some unidentified fluid.

3.5 Trauma theory
From the late 1800s until the 1920s, cancer was thought to be caused by trauma.

3.6 Parasite theory
Till the 18th century, scientists believed that cancer was contagious and spreads through parasite.

4. Type of Cancer
There are more than 100 types of cancer. Cancer is described by where in the body it originated; type of tissue it originated in, and type of cell it started in. For example, breast cancer is breast-originated cancer, if it spreads to a new organ, such as the lung, the tumor is called metastatic breast cancer, not lung cancer [13]. Cancers that occur in epithelial tissues are called Carcinomas, those that originate in connective tissues are called Sarcomas, and those that develop in blood-forming tissue are Leukemias (blood cells) and Lymphomas (lymphatic system) [13]. Cancers that originate in squamous cell found in epithelial tissue are called Squamous cell carcinomas; those that occur in edematous cells that are glandular are called Adenocarcinomas. Sarcomas that develop in fat cells are called Liposarcomas, and those that develop in bone cells are called Osteosarcomas [13].

5. Prevalence of Cancer
There are variations in the patterns, trends, and rates of cancer throughout the world. These variations are largely due to variations in the patterns of food and drink, of physical activity, and of body composition in the human population [29]. The prevalence of cancer vary by sex, for example, cancer is prevalent in men than women like it. Geographical and socioeconomic differences exist for the most common cancers. In low-income countries, the most prevalent cancers include those of which infectious agents are a major cause, e.g. cervix cancer, while in high-income countries, they include hormone-related cancers, e.g. breast cancer. In high-income countries, and among men, prostate cancer is the most common type, followed by cancers of the lung, stomach, colon, and rectum while in women, breast cancer is the most common type followed by cancers of the lung, colon and rectum, and endometrium. In low-income countries, and among men, lung cancer is the most common type, followed by cancers of the esophagus, stomach, and liver while breast cancer is also the most frequent type among women followed by cancers of the lung, stomach, and cervix [29]. Still, there are differences between races in the prevalence of cancer: in the United States, for example, the development of bladder cancer is higher in white people than black people; white women have a higher risk of breast cancer than black, Asian, Hispanic and Native American women; and African Americans, especially men, have the highest risk of developing and dying from cancer in the United States. Differences in diet and exercise, unequal access to medical care and exposure to carcinogen are suggested to be responsible for between-race differences [13].

6. Etiology of Cancer
Cancer is multifactorial in origin [30] with a complex mechanism of development [13]. Studies showed that people of 45 years and above have a higher risk of developing the
disease than others. Some risk factors that increase the likelihood of developing cancer are provided through epidemiological studies of the human population. Some of these risk factors according to [13] are mentioned hereby.

6.1 Carcinogens
1. Tobacco smoke; e.g. cigars, pipes, smokeless tobacco, etc.
2. Diet; e.g. saturated fats, high salt intake, alcohol, refined foods, and sugar, etc.
3. Pathogens; e.g. human papillomavirus (HPV), hepatitis B&C virus, HIV etc.
4. Radiation; e.g. ultraviolet radiation, X rays, radon gas, therapeutic radiology, etc.

6.2 Steroid hormones
Steroid hormones; e.g. estrogen, testosterone, hormone replacement therapy, etc.

6.3 Population demographics
Population demographics; e.g. age, race, sex, and economy.

6.4 Hereditary Factor
Hereditary factors; e.g. inherited mutated breast cancer anti-tumor (BRCA1 or BRCA2) and DNA repairing (MSH2, MLH1, etc.) genes. An inherited gene mutation is the one that is present in the germ cells which formed the fetus and thus can be passed from one generation to the next. Somatic or sporadic mutation which is not present in the germ cells and thus not transmitted to next generation [13]. About 70 genes of the cancer genes are associated with hereditary mutations while 342 of the cancer genes are associated with somatic mutations [32]. For example, BRCA1 and BRCA2 are human genes that produce anti-tumor proteins which help repair damaged DNA and thus ensuring the stability of the cell’s genetic material. When either of these genes is mutated such that its protein product is not made or malfunctioned, DNA damage may not be repaired properly thereby causing additional genetic alterations that can lead to cancer. BRCA1 and BRCA2 mutations account for about 20 to 25 percent of hereditary breast cancers, about 5 to 10 percent of all breast cancers and around 15 percent of ovarian cancers. The effects of mutations in BRCA1 and BRCA2 are seen even when a person’s second copy of the gene is normal [33]. They cause damage to DNA of the cell either by covalently binding to Purines, pyrimidines and phosphodiester bonds of DNA, the formation of pyrimidine dimers in DNA, binding to Purines, pyrimidines and phosphodiester bonds of DNA, or insertion into the host genome [14]. Deoxyribonucleic acid (DNA) is a sequence of DNA that has been altered or mutated [31]. This is a sequence of DNA that has been altered or mutated [31]. It can be passed from one chromosome in a pair and in order for a gene to stop working completely and potentially lead to cancer, both copies must be mutated [13]. Carcinogenesis is usually a multistep process [38] that can be discussed in the context of such fundamental changes, in cell physiology that together determines malignant phenotype, as oncogenes, mutated tumor-suppressors genes, inappropriately-activated telomerase [16], mutated genes that regulate apoptosis [39] and epigenetic perturbation.

8. Oncogenes
This is a sequence of DNA that has been altered or mutated from its original form, the Proto-oncogene [40], causing a spontaneous cell proliferation [13]. Proto-oncogenes are normal genes that control cell growth and division by coding for proteins that pass the message in a succession from the exterior of the cell to its nucleus [39]. Most hematological and solid tumors are caused by either activation of certain genes that promote carcinogenesis, normally called oncogenes. Oncogenes are responsible for the production of transcription factors, growth factors, receptors, genes involved with chromatin remodeling and apoptosis regulatory factors [41]. It is generally accepted that oncogenes are main cancer-causing genes. Many studies done in mice model systems have explained the role of oncogenes in carcinogenesis, cancer progression and suppression. For example [42] cultured single cells extracted from the mammary gland of non-transgenic mice and examined the role of oncogenes in carcinogenesis and cancer suppression in primary cancer cells.

8.1 Tumor suppressor genes
Tumor suppressor genes are genes that regulate the growth of cells. When these genes are functioning properly, they can prevent and inhibit the growth of tumors. There are 3 main types of tumor suppressor genes, namely, one that slows down and stops cell division; one that fixes damages in DNA when cells divide and the third is the one that stimulates cells death, apoptosis [43]. They encode for proteins that are involved in inhibiting the proliferation of cells crucial to normal development and differentiation and thus enables them to stop the uncontrolled growth of cancer cells. However genetic damage or mutation that occurs to these genes may contribute to the development of a cancerous tumor [44]. Several tumor suppressor genes have been investigated for a role in the etiology of cancer; for example loss-of-function mutation in a tumor suppressor gene NF1, which encodes Neurofibrinom (a Ras GTPase-activating protein; RasGAP) has been reported as a cause of inherited cancer known as neurofibromatosis type 1 [45]. Neurofibromatosis type 1 has been associated with the development of glioma [46].
Meanwhile, a mutation in the tumor suppressor gene RB which is constitutively expressed in non-neoplastic cells has been associated with retinoblastoma – a childhood retinal cancer [47].

8.2 Genes that regulate apoptosis
Apoptosis is a programmed cell death that normally involved in an organism’s development and maintenance [48]. Apoptosis may be induced when a cell becomes abnormal especially during tumor and perhaps malignancy therein causing the abnormal cell to die. However, the abnormal cell can fail to die due to a mutation that leads either to malfunctioning of such a tumor suppressor gene as p53 gene, a gene that can trigger apoptosis or over-expression of such proto-oncogene as bcl-2 which produces large quantities of bcl-2 protein which inactivate apoptotic program. Malignant lymphomas resulting from transformed B-lymphocyte are caused by the mutation of the bcl-2 gene [39].

8.3 Telomerase Activities
This is RNA-associated enzyme that synthesis telomeres [49], specialized sequences of DNA found at the tip of chromosomes which prevent the continuous loss of DNA during the course of replication in a cell [50]. A normal cell has a replication span and stops dividing when old. Telomeres partly regulate the process of aging and dying of a cell as they shorten every time chromosomes are replicated and the cell divides. Once telomeres become shortened to a certain size, the cell reaches a crisis point and then prevented from dividing further and dies thereby serving as a tumor suppressor by inducing cell death [51]. Conversely, the shortening of telomeres in a cell undergoing replication can be prevented either by oncogenic expression or inactivation of tumor suppression activity as in a cell undergoing malignant transformation. In the transformed cell, telomeres do shorten but as the crisis point nears, enzyme telomerase which was formerly inactive become activated and thus prevents telomeres from shortening further thereby prolonging the life of the cell. Indeed, telomerase activity has been detected in more than 90% of human tumors including breast, colon, prostate and ovarian cancers [52].

8.4 Epigenetic perturbations
This is the process by which gene expression can be altered without changing the DNA sequence [52]. More recently it has become clear that epigenetic alterations in the CpG islands near the promoter regions of tumor suppressor genes may also contribute to genetic instability. Many published studies have shown that epigenetic alterations at the loci that control different specific transcription factors may result in misinterpretation of some histone codes and producing factors that can dysregulate cell cycle control machinery and cause cancer. For example, the carcinogenic potentials of the fusion of carboxyl-terminal of Plant homeodomain (Ph.D.) fingers (JARIDIA) with the transactivating domain of nucleoporin 98 (NUP98) to produce JARIDIA –NUP98 has been studied [53]. The study shows that chromosomal instability resulting from translocations may lead to the production of factors that can disrupt methylation status or methylation-readout areas of some important loci in the DNA and cause cancer. Thus epigenetic perturbation may have some important implication in cancer initiation [53].

9. Therapy of Cancer [54]
9.1 Surgery and use modern technology
Ancient surgeons knew that cancer would usually come back after it was removed by surgery. Many people even today consider that many types of cancers are incurable and may delay consulting a doctor in the early stage. After anesthesia was invented in 1846, surgeons Billroth, Handley and Halsted led cancer operations by removing the entire tumor together with lymph nodes. Understanding the mechanism(s) of cancer spreading became a key element in recognizing the limitations of cancer surgery. At the beginning of 1970s, progress in ultrasound (sonography), computed tomography (CT scans), magnetic resonance imaging (MRI scans) and positron emission tomography (PET scans) have replaced most exploratory operations. Using miniature video cameras and endoscopy, surgeons can remove colon, esophagus and bladder tumors through tubes. Lasers also can be used to cut the tumor tissue of cervix, larynx, liver, rectum, skin and other organs.

9.2 Chemotherapy
During the last decades of the 20th century, surgeons developed new methods for cancer treatment by combining surgery with chemotherapy and/or radiation. Roentgen discovered Xrays after 50 years of anesthesia was discovered. Later doctors identified that nitrogen mustard can kill rapidly proliferating lymphoma cancer cells. Now new approaches are being studied to reduce the side effects of chemotherapy including use of:
1. New combinations of drugs.
2. Liposomal and monoclonal antibody therapy to target specific cancer cells.
3. Chemoprotective agents to reduce chemotherapy side effects.
4. Hematopoietic stem cell transplantation.
5. Agents that overcome multidrug resistance.

9.3 Hormonal therapy
In 1878 Thomas Beatson discovered that the breasts of rabbits stopped producing milk after he removed ovaries. Later scientists identified that dramatic regression of metastatic prostate cancer following removal of the testes. Now new classes of drugs (aromatase inhibitors, LHRH analogs) are being used to treat prostate and breast cancers. How hormones influence growth of cancer has guided progress in developing as well as reducing the risk of breast and prostate cancers.

9.4 Radiation therapy
In 1896 Roentgen discovered “X-ray” and after 3 years later radiation was used for cancer diagnosis and in treatment. In the early 20th century, researchers discovered that radiation could cause cancer as well as cure it. Now several radiation therapies are being used, these include:
1. Conformal proton beam therapy (proton beam will be used for killing tumor cells instead of X-rays).
2. Stereotactic surgery and stereotactic therapy (gamma knife can be used to deliver and treat common brain tumor).
3. Intra-operative radiation therapy (cancer has been removed surgically followed by radiation to the adjacent tissues).
9.5 Adjuvant therapy
It is the use of chemotherapy after surgery to destroy the few remaining cancer cells in the body. Adjuvant therapy was used in colon and testis cancers.

9.6 Targeted cancer treatment
Until the late 1990’s most of the drugs used in cancer therapy worked by killing cancer cells. Unfortunately, chemotherapy agents used also killed some normal cells and had a greater effect on cancer cells.

9.7 Immunotherapy
Use of biological agents that mimic some of the natural signals that the body uses to control tumor growth is called immunotherapy. These natural biological agents can now be produced in the laboratory including interferons, interleukins, cytokines, endogenous angiinhibitors, and antigens. At present scientists are developing vaccines to boost the body’s immune response against cancer cells.

10. Future Cancer treatment
The growth in knowledge of cancer biology has led to remarkable progress in cancer early detection, treatment and prevention in recent years. Cancer research is currently advancing on so many fronts that are highlighted below.

10.1 Antiangiogenic chemotherapy
Recently, in many clinical trials, angiinhibitors were also being used in combination with conventional chemotherapy. Clinical trials generally combine very low-dose of chemotherapy followed by angiinhibitor therapy. Combination of angiinhibitors will need to be tested vigorously in the future, as single angiinhibitors are approved for use of cancer. For example, it is very important to know whether bisphosphonates are synergistic with certain natural angiinhibitors such as angiostatin, endostatin, thrombospondin, arrested, canstatin tumstatin, etc. It is also better to test food that has high levels of natural angiinhibitors for prevention of cancer.

10.2 More targeted treatments
As more is learned about the molecular biology of cancer cell, researchers developed new classes of molecules such as antisense oligodeoxynucleotides and small interfering RNA (siRNA) for the treatment of cancer.

10.3 Nanotechnology
It is the use of extremely tiny particles for diagnostic imaging to more accurate location of tumors for delivering drugs more specifically and effectively into cancer cells.

11. Enzyme supplement of Cancer
Some cancer patients that are difficult to be treated with dietary means due to digestion disorders can be supplemented with enzyme for the efficient digestion of food. Enzyme supplement will give raw foods thorough digestion with less of the body’s own resources. Primarily the enzymes taken with meals assist the body in getting all the nutrients out of the food for healing and restoring the body to normal function. Recently, in a study in which supplemental digestive enzymes were tested in vitro, the digestive enzymes improved the digestibility and bio accessibility of proteins and carbohydrates in the lumen of the small intestine, not only under impaired digestive conditions but also in healthy human digestion.[15]. This hypothesis was tested in a clinical trial in which an oral enzyme supplement was taken by patients with stage III multiple myeloma and a placebo taken by another patient with a similar case, thereby resulted in prolonging the survival time for patients who took the oral enzymes to 83 months compared to 47 months survival time for the patients that took the placebo.[15].

11.1 Some mechanism by which foods and their bioactive substance offer protection against Cancers.
There are many mechanisms by which foods are protective against cancers. Some of these are explained below.

11.2 Vegetables
Vegetables provide a large amount of potentially cancer-preventive substances, including several such antioxidant nutrients as carotenoids and vitamin C, dietary fiber, as well as such phytochemicals as glucosinolates, dithiolthiones, indoles, chlorophyll, flavonoids, allyl-sulfides, and phytoestrogens. Phytochemicals might influence cancer risk through their antioxidant activities, modulation of detoxification enzymes and stimulation of the immune system, antiproliferative activities, and/or modulation of steroid hormone concentration and hormone metabolism and, other actions. Cruciferous vegetables contain glucosinolates, which are transformed by food preparation into isothiocyanates (ITCs), which alter the metabolism of carcinogens. Indoles and ITCs, two major glucosinolate breakdown products, attenuate the effects of polycyclic aromatic hydrocarbons and nitrates via induction of glutathione-S-transferases (GSTs) and inhibition of cytochrome P450 isoenzymes, respectively. Certain hydrolysis products of glucosinolates, including indoles and isothiocyanates, have shown anti-carcinogenic properties in laboratory experiments and in diets in live experiments in animals.[56].

11.3 Fruits
Fruits, in particular, citrus fruits, are sources of vitamin C and other antioxidants, such as phenols and flavonoids, as well as potentially bioactive phytochemicals. Vitamin C traps free radicals and reactive oxygen molecules, protecting against oxidation damage. It also regenerates other antioxidant vitamins such as vitamin E. Vitamin C also inhibits the formation of carcinogens and protects DNA from mutagenic attack.[29]. The phytochemical antioxidants contained in fruit could reduce free radical damage generated by inflammation. A single study reported that apples given in physiological quantities inhibited carcinogen-induced mammary cancer in rodents in a dose-response manner.[57] In addition, grape extracts and auraptene found in citrus fruit have shown protective effects against the development of hepatocellular carcinoma in rats.[58].

11.4 Food containing vitamin E
Vitamin E is an antioxidant that has been reported to prevent DNA damage, enhance DNA repair, prevent lipid peroxidation, and prevent activation of carcinogens such as nitrosamines. Vitamin E protects vitamin A and selenium in the body. In addition to acting as a free-radical scavenger, vitamin E enhances the body’s immune response, which may play a role in cancer defenses.[59].
11.5 Pulses (legumes)
Pulses (legumes), particularly soya foods, contain various compounds that may have anticancer effects, including protease inhibitors, saponins, and phytoestrogens, such as genistein and daidzein, which are found in high concentrations in soya. These compounds could plausibly influence estrogen metabolism. They have also been shown to have antioxidant effects, inhibit the growth of blood vessels to a tumor, and may influence apoptosis and cell growth. Phytoestrogens in pulses and soya can have an androgenic effect, potentially inhibiting testosterone-induced growth of the prostate. In addition, laboratory experiments have shown that genistein slows down the development of stomach cancers promoted by sodium chloride by increasing apoptosis, and lowering cell proliferation and blood vessel growth.

12. Conclusion
Cancer develops when a normal cell in a particular part of the body begin to grow out of control. In the past decade's research has reported a substantial volume of information about gene and protein and their role in the production of the cancer cell. In fact, the role of the mutated gene in the cancer cell was one of the most important discoveries. A diet that is good for preventing or reducing cancer risk should contain foods from the plant and marine origins, such as fruit and vegetables, legumes which are an excellent source of the mineral, vitamins, phytochemical, antioxidant, phytoestrogens that would encourage the growth of probiotics and be supplemented with oral digestive enzyme. However, by identifying all environmental factors and pivotal genes, this gives us a comprehensive map for further effort to reduced cancer in the future.

13. Recommendations
1. Advanced clinical trials of these diets should be carried out to prove their benefits against and or efficacy in the treatment of cancer in humans.
2. Men should be carefully planned to ensure optimal nutrition with calories restriction i.e. meal should be nutrients dense and calories less dense.
3. Awareness on the disease in respect to the cause and preventative measure should be carried out.
4. The regular medical check-up should be done as early detection of the disease is paramount to cure.

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15. References

