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Review Article

Cancer: Insights into Epidemiology, Classification, Aetiology, Diagnosis, Prevention, and Cancer Chemotherapy

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Abstract: **Background:** Cancer is a major public health problem in many parts of the world. One in 4 deaths in the United States is due to cancer which is second only to cardiovascular disease as the leading cause of death, in the United Kingdom, it is the leading cause of death. There is increasing interest in strategies for cancer prevention due to the steady increase in global cancer incidence with its associated morbidity and mortality, together with the healthcare costs of treatment. **Objectives:** The aim of the current review is a high light on the cancer epidemiology, classification, aetiology, diagnosis, prevention, cancer chemotherapy, and natural products uses to decrease the harmful effect of chemotherapy. Cancer is a disease in which a group of cells displays uncontrolled growth and invasion that destroy adjacent tissues, and sometimes metastasize to other locations in the body. Cancers are caused by a series of mutations. Cancer cases are due to 5-10% genetics, and 90-95% environmental factors which including; infections, diet lack of physical activity, and obesity, stress, tobacco, radiation, and environmental pollutants. Cancer symptoms are local, metastatic, and systemic symptoms. Local symptoms can include lumps or swelling, hemorrhage, ulceration and pain. Metastatic symptoms include enlarged lymph nodes, hepatomegaly, splenomegaly, neurological symptoms, and fracture of affected bones. Systemic symptoms occur due to distant effects of the cancer that are not related to direct or metastatic spread. Some of these effects can include weight loss, poor appetite, cachexia, fatigue, excessive sweating, anemia, and other specific conditions. Human cancer classification is currently based on the idea of cell of origin, light and electron microscopic attributes of the cancer. Chemotherapy is used to produce complete cure, prolong life or to reduce symptoms of cancer. It may use one drug at a time or several drugs at once. The most common one classify these agents according to their mechanism of action into alkylation agents, antimetabolites, antimicro- tubules, topoisomerase inhibitors and cytotoxic antibiotics. To decrease the dose and toxicity and increase the efficacy of chemotherapy regimens, various approaches were investigated. One of them was the search for natural agents with anticancer properties that can be used in combination with the traditional anticancer agents . Many of chemoprotective plants are used with the traditional anticancer agents. **Conclusion:** It can be concluded that cancer is a disease in which a group of cells displays uncontrolled growth and invasion that destroy adjacent tissues. The causes of cancer are due to genetics, and environmental factors. Cancer symptoms are local, metastatic, and systemic symptoms. Chemotherapy uses to produce complete cure, prolong life or to reduce symptoms of cancer. Many of chemoprotective natural products are used with the traditional anticancer agents. So, the patients should be advised to take one of natural products while they are treated with chemotherapy to decrease its harmful effects.

Keywords: Cancer overview, Epidemiology, Classification, Aetiology, Diagnosis, Cancer prevention, Cancer chemotherapy.

1. INTRODUCTION

Cancer is characterized by unregulated growth of some body cells. The use of the traditional anticancer agents such as 5-fluorouracil, methotrexate, adriamycin and cisplatin was faced by their harmful adverse effects (El-Sayyad *et al.*, 2009) . In an attempt to decrease the effective chemotherapeutic dose and thereby side effects, various approaches were tried including the use of various lines of targeted therapy, complementary and alternative

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medicine. One of these lines was the search for natural compounds with anticancer properties that can be used in combination with the traditional anticancer agents (Al-Harthi *et al.*, 2014).

Human cancer classification is currently based on the idea of cell of origin, light and electron microscopic attributes of the cancer. The integrated model of cancer classification are morphology, cancer stem cell contributions, genetic, and functional attributes of cancer. Integrated cancer classification models could eliminate the unclassifiable cancers. Future cancer treatment may be advanced by using an integrated model of cancer classification (Idikio, 2011).

Cancer is a broad term that includes diseases in which a group of cells displays uncontrolled growth and invasion that destroy adjacent tissues, and sometimes metastasize to other locations in the body. These malignant properties of cancer differentiate it from benign tumors, which do not invade the surrounding tissues or metastasize to the distant organs (Hanahan and Weinberg, 2011).

The causes of cancer were subdivided into two main categories: those with an environmental and those with a hereditary genetic cause. Cancer is primarily an environmental disease, though genetics influence the risk of some cancers. The environmental causes are including; infections, diet lack of physical activity, and obesity, stress, tobacco, radiation, and environmental pollutants (Anand *et al.*, 2008). These environmental factors cause abnormalities in the genetic material of cells. Cell reproduction is a complex process that is regulated by several classes of genes, including oncogenes and tumor suppressor genes. Hereditary or acquired abnormalities in these regulatory genes can lead to the development of cancer. A small percentage of malignant tumors are entirely hereditary (Samadder *et al.*, 2015).

The presence of cancer can be suspected on the basis of symptoms or findings on radiological investigations. Definitive diagnosis of cancer, however, requires the microscopic examination of a biopsy specimen. Treatment of cancer includes chemotherapy, radiotherapy and surgery. The prognosis is influenced by the type of cancer and the extent of disease. While cancer can affect people of all ages, the overall risk of developing cancer increases with age (Jemal *et al.*, 2011).

2. Epidemiology of Cancer:

Cancer is a major public health problem in the United States and many other parts of the world. One in 4 deaths in the United States is due to cancer. In the United States, cancer is second only to cardiovascular disease as the leading cause of death (Siegel *et al.*, 2016). In the United Kingdom, it is the leading cause of death (Wallace and Kulu, 2015). In many third world countries, cancer incidence appears much lower, most likely because of the higher death rates due to infectious diseases or injury. With the increased control over malaria and tuberculosis in some third world countries, the incidence of cancer is expected to rise. In the Eastern Mediterranean region, for example, cancer incidence is expected to increase by 100% to 180% in the next 15 years due to the increase in life expectancy, an increasing proportion of elderly people, and the successful control of childhood disease (Khatib and Aljurf, 2008) .

Cancer incidence varies significantly between civilized and rural areas. Some types of cancer are considered as civilization disorders such as cancer colon and rectum (Watson and Collins, 2011) .

Cancer epidemiology closely mirrors risk factor spread in various countries. Hepatocellular carcinoma is rare in the western countries but is the main type of cancer in China and neighbouring countries, most likely due to the endemic presence of hepatitis B and aflatoxin in that population. Similarly, with tobacco smoking becoming more common in various third world countries, lung cancer incidence has increased in a parallel fashion (Jemal *et al.*, 2011).

3. Classification of Cancer:

Classification of cancer is important to determine the appropriate treatment and to predict the prognosis. Cancer classification is usually made according to the site of origin of the malignant cells, the histopathological analysis (called grading) and the extent of the disease (called staging) (Mirsadraee *et al.*, 2012).

3.1. Classification According To the Site of Origin of Cancer:

This classification describes the type of tissue in which the cancer cells begin to develop.

There are some common examples of site of origin classification as follows (Berman, 2004) :

- Adenocarcinoma– originates in glandular tissue.
- Blastoma– originates in embryonic tissue of organs.
- Carcinoma– originates in the epithelial tissue.
- Leukemia– originates in tissues that form blood cells.
- Lymphoma– originates in lymphatic tissue.
- Myeloma– originates in bone marrow.
- Sarcoma– originates in connective or supportive tissue (e.g., bone, cartilage, muscle).

3.2. Classification According To the Tumor Grading:

Grading involves examination of the tumor tissues that have been obtained through biopsy under a microscope. The abnormality of the cells determines the grade of the tumor. Increasing abnormality increases the grade, from 1– 4. Cells that are well differentiated closely resemble mature, specialized cells. Cells that are undifferentiated are highly abnormal, that is, immature and primitive (Sehnal *et al.*, 2011) .

3.3. Classification According To Cancer Staging:

Staging is the classification of the extent of the tumor. There are several types of staging methods. The tumor, node, metastases (TNM) system is the most widely used for cancer staging. It classifies cancer by tumor size (T), the degree of regional spread or involvement of the regional lymph nodes (N), and the presence of distant metastasis (M). A numerical system also is used to classify the extent of disease where stage 0 represents carcinoma in situ, stage I represents cancer limited to the tissue of origin with evidence of tumor growth, stage II represents limited local spread of cancerous cells, stage III represents extensive local and regional spread, and stage IV represents distant metastasis (Mirsadraee *et al.*, 2012).

4. Aetiology of Cancer:

Cancer is primarily an environmental disease with 90-95% of cases attributed to environmental factors and 5-10% due to genetics. Common environmental factors that contribute to cancer death include: tobacco (25-30%), diet and obesity (30-35%), infections (15-20%), radiation (both ionizing and non ionizing, up to 10%), stress, lack of physical activity, and environmental pollutants (Anand *et al.*, 2008) .

4.1. Chemicals:

Cancer pathogenesis is attributed to DNA mutations that impact cell growth and metastasis. Substances that cause DNA mutations are known as mutagens. Mutagens that cause cancer are known as carcinogens. Particular substances have been linked to specific types of cancer. Tobacco smoking is associated with many forms of cancer and causes 90% of lung cancer (Sasco *et al.*, 2004) .

Decades of research have demonstrated the link between tobacco use and cancer in the lung, larynx, head, neck, stomach, bladder, kidney, esophagus and pancreas. Tobacco smoke contains over fifty known carcinogens, including nitrosamines and polycyclic aromatic hydrocarbons. Tobacco is responsible for about one in three of all cancer deaths in the developed world and about one in five worldwide. Lung cancer death rates in the United States have mirrored smoking patterns, with increase in smoking followed by dramatic increase in lung cancer death rates and decrease in smoking followed by decrease in lung cancer death rates in men. However, the number of smokers worldwide is still rising, leading to what some organizations have described as the tobacco epidemic (Proctor, 2004).

Cancer related to one's occupation is believed to represent between 2– 20% of all cases. Every year, at least 200,000 people die worldwide from cancer related to their workplace. Currently, most cancer deaths caused by occupational risk factors occur in the developed world. It is estimated that approximately 20,000 cancer deaths and 40,000 new cases of cancer each year in the U.S. are attributable to occupation. Millions of workers run the risk of developing cancers such as lung cancer and mesothelioma from inhaling asbestos fibers and tobacco smoke, or leukemia from exposure to benzene at their workplaces (Irigaray *et al.*, 2007) .

4.2. Diet and exercise:

Diet, physical inactivity, and obesity are related to approximately 30– 35% of cancer cases(Anand *et al.*, 2008). In the United States, excess body weight is associated with the development of many types of cancer and is a factor in 14– 20% of all cancer death. Physical inactivity is believed to contribute to cancer risk not only through its effect on body weight but also through negative effects on immune system and endocrine system (Kushi *et al.*, 2012).

Diets that are low in vegetables, fruits and whole grains, and high in processed or red meat are linked with many types of cancer. A high salt diet is linked to gastric cancer; aflatoxin B1, a frequent food contaminate, with liver cancer and Betel nut chewing with oral cancer (Park *et al.*, 2008). This may partly explain differences in cancer incidence in different countries. For example, gastric cancer is more common in Japan with its high salt diet and colon cancer is more common in the United States. Immigrants develop the risk of their new country, often within one generation, suggesting a substantial link between diet and cancer (Brenner *et al.*, 2009).

4.3. Infection:

A virus that can cause cancer is called an oncovirus. These include human papilloma virus (cervical carcinoma), Epstein-Barr virus (B-cell lymphoproliferative disease and nasopharyngeal carcinoma), Kaposi's sarcoma herpesvirus (Kaposi's Sarcoma and primary effusion lymphomas), hepatitis B and hepatitis C viruses (hepatocellular carcinoma), and Human T-cell leukemia virus-1 (T- cell leukemias). Bacterial infections may also increase the risk of cancer, as seen in Helicobacter pylori-induced gastric carcinoma (Pagano *et al.*, 2004) . Parasitic infections strongly associated with cancer include Schistosoma haematobium (squamous cell carcinoma of the bladder) and the liver flukes, Opisthorchis viverrini

and Clonorchis sinensis (cholangiocarcinoma) (Vassilis *et al.,* 2010).

4.4. Radiation:

Up to 10% of invasive cancers are related to radiation exposure, including both ionizing radiation and non-ionizing radiation. Additionally, the majority of non-invasive cancers are non- melanoma skin cancers caused by non-ionizing radiation from ultraviolet radiation (Anand *et al.,* 2008). Ionizing radiation hits molecules within cells randomly. If it strikes a chromosome, it can break the chromosome resulting in an abnormal number of chromosomes, inactivate one or more genes, delete parts of the DNA sequence, cause chromosome translocations or cause other chromosomal abnormalities. The major damage results in cell death but smaller damage may leave a stable, partly functional cell that may be capable of proliferating and developing into cancer, especially if tumor suppressor genes were damaged by radiation (Danaei *et al.,* 2005) .

4.5. Heredity:

Less than 0.3% of the population are carriers of a genetic mutation which has a large effect on cancer risk. These genetic mutations cause less than 3– 10% of all cancer (Roukos, 2009).

Some of these syndromes include:

- Certain inherited mutations in the genes BRCA1 and BRCA2 with a more than 75% risk of breast cancer and ovarian cancer.
- Tumors of various endocrine organs in multiple endocrine neoplasia (types 1, 2a, 2b)
- Li-Fraumeni syndrome (various tumors such as osteosarcoma, breast cancer, soft
- tissue sarcoma, brain tumors) due to mutations of p53.
- Turcot syndrome (brain tumors and colonic polyposis)
- Familial adenomatous polyposis an inherited mutation of the APC gene that leads to early
- onset of colon carcinoma.
- Hereditary nonpolyposis colorectal cancer (HNPCC, also known as Lynch syndrome) can
- include familial cases of colon cancer, uterine cancer, gastric cancer, and ovarian cancer.
- Retinoblastoma, when occurring in young children, is due to a hereditary mutation
- in the retinoblastoma gene.
- Down syndrome patients, who have an extra chromosome 21, are known to develop malignancies such as leukemia and testicular cancer (Roukos, 2009).

4.6. Physical trauma:

Physical trauma resulting in cancer is relatively rare. Long- term application of hot objects to the body may cause cancer. It is possible that repeated burns on the same part of the body may produce skin cancer; especially if carcinogenic chemicals are also present. Frequently drinking hot tea may produce esophageal cancer. Generally, it is believed that the cancer arises, or a pre-existing cancer is encouraged, during the process of repairing the trauma, rather than the cancer being caused directly by the trauma. However, repeated injuries to the same tissues might promote excessive cell proliferation, which could then increase the cancerous mutations (Rigby *et al.,* 2002).

4.7. Hormones:

Some hormones participate in the development of cancer by promoting cell proliferation. Hormones are important agents in sex- related cancers such as cancer of the breast, endometrium, prostate, ovary and testis and also of thyroid cancer and bone cancer (Stanczyk *et al.,* 2015).

An individual's hormone levels are mostly determined genetically, so this may explain the presence of some cancers that run in families that do not seem to have any cancer-causing genes. For example, the daughters of women who have breast cancer have significantly higher levels of estrogen and progesterone than the daughters of women without breast cancer. These higher hormone levels may explain why these women have higher risk of breast cancer, even in the absence of a breast-cancer gene. However, non- genetic factors are also relevant: obese people have higher levels of some hormones associated with cancer and a higher rate of those cancers. Women who take hormone replacement therapy have a higher risk of developing cancers associated with those hormones. Some treatments and prevention approaches depend on reducing hormone levels, and thus discouraging hormone-sensitive cancers (Folkerd and Dowsett, 2013).

5. Pathophysiology of cancer:

Cancers are caused by a series of mutations. Each mutation alters the behavior of the cells. Cancer is due to failure of regulation of tissue growth. In order for a normal cell to transform into a cancer cell, the genes which regulate cell growth and differentiation must be altered (Croce, 2008).

Large scale mutations involve the deletion or gain of a portion of a chromosome. Genomic amplification occurs when a cell gains many copies of a small chromosomal locus, usually containing one or more oncogenes and adjacent genetic material. Translocation occurs when two separate chromosomal regions become abnormally fused, often at a

characteristic location. A well-known example of this is the Philadelphia chromosome, or translocation of chromosomes 9 and 22, which occurs in chronic myeloid leukemia, and results in production of the BCR-abl fusion protein, an oncogenic tyrosine kinase (Nelson *et al.*, 2004).

Small-scale mutations include point mutations, deletion and insertion which may occur in the promoter region of a gene and affect its expression, or may occur in the gene's coding sequence and alter the function or stability of its protein product. Disruption of a single gene may also result from integration of genomic material from a DNA virus or retrovirus resulting in the expression of viral oncogenes in the affected cell and its daughter cells (Merlo *et al.*, 2006).

Replication of the enormous amount of data contained within DNA of living cells may result in some errors (mutations). Complex error correction safeguards the cell against cancer. If significant error occurs, the damaged cell cans self destruct through apoptosis. If the error control processes fail, then the mutations will be passed along to daughter cells. Some environmental factors such as carcinogens, repeated physical injury, heat, ionising radiation or hypoxia make errors more likely to arise and propagate (Nelson *et al.*, 2004) . The errors which cause cancer are self-amplifying and compounding, for example:

- A mutation in the error-correcting machinery of a cell might cause that cell and its children to accumulate errors more rapidly.
- A further mutation in an oncogene might cause the cell to reproduce more rapidly and more frequently than its normal counterparts.
- A further mutation may cause loss of a tumour suppressor gene, disrupting the apoptosis signalling pathway and resulting in the cell becoming immortal.
- A further mutation in signaling machinery of the cell might send error-causing signals to nearby cells (Croce, 2008).

The transformation of normal cell into cancer is a chain reaction caused by initial errors, which compound into more severe errors, each progressively allowing the cell to escape the controls that limit normal tissue growth. These forces work against the body's design. Once cancer has begun to develop, this ongoing process, termed clonal evolution drives progression towards more invasive stages (Merlo *et al.*, 2006).

6. Clinical Manifestations of Cancer:

Cancer symptoms can be divided into three groups:

- **Local symptoms:** are restricted to the site of the primary cancer.
  They can include lumps or swelling, hemorrhage (bleeding from the skin, mouth or anus), ulceration and pain. Although local pain commonly occurs in advanced cancer, the initial swelling is often painless.
- **Metastatic symptoms:** are due to the spread of cancer to other locations in the body. They can include enlarged lymph nodes, hepatomegaly or splenomegaly which can be felt in the abdomen, pain or fracture of affected bones and neurological symptoms.
- **Systemic symptoms:** occur due to distant effects of the cancer that are not related to direct or metastatic spread. Some of these effects can include weight loss, poor appetite, cachexia, fatigue, excessive sweating (especially night sweats), anemia and other specific conditions termed paraneoplastic phenomena. These may be mediated by immunological or hormonal signals from the cancer cells. None of these symptoms are diagnostic, as many of these symptoms commonly occur in patients who do not have cancer (Park *et al.*, 2008).

7. Diagnosis of cancer:

Most cancers are initially recognized either because signs or symptoms appear or through screening. Neither of these lead to a definitive diagnosis. People with suspected cancer are investigated with blood tests, X-rays, CT scans and endoscopy. The definitive diagnosis must be confirmed by histological examination of the cancerous cells by a pathologist. This indicates the type of cell that is proliferating, its histological grade, genetic abnormalities and other features of the tumor. Together, this information is useful to evaluate the prognosis of the patient and to choose the best treatment. Cytogenetics and immunohistochemistry are other types of testing that the pathologist may perform on the tissue specimen. These tests may provide information about the molecular changes that has happened in the cancer cells and may thus also indicate the prognosis and the appropriate treatment (Jemal *et al.*, 2011) .

8. Prevention of cancer:

Cancer prevention is defined as active measures to decrease the incidence of cancer. The vast majority of cancer risk factors are environmental or lifestyle-related, thus cancer is largely a preventable disease. Greater than 30% of cancer is preventable by avoiding the risk factors including: tobacco, overweight or obesity, low fruit and vegetable intake,

physical inactivity, alcohol, sexually transmitted infections, and air pollution (Danaei *et al.*, 2005) .

8.1. Dietary:

Dietary recommendations to reduce the risk of developing cancer, including reducing intake of foods and drinks that promote weight gain (energy-dense foods and sugary drinks), eating mostly foods of plant origin, limiting intake of red meat and avoiding processed meat, limiting consumption of alcoholic beverages, and reducing intake of salt and avoiding mouldy cereals (grains). There are many reports that reduced meat consumption is associated with decreased risk of colon cancer, and that consumption of coffee is associated with a reduced risk of liver cancer (Larsson and Wolk, 2007). Studies have linked consumption of grilled meat to an increased risk of stomach cancer, colon cancer, breast cancer and pancreatic cancer, a phenomenon which could be due to the presence of carcinogens in foods cooked at high temperatures (Zheng and Lee, 2009). Some studies have found that consuming lots of fruits and vegetables has little if any effect on preventing cancer (Boffetta *et al.*, 2010). Another study showed that consumption of a plant-based diet and lifestyle changes resulted in a reduction in cancer markers in a group of men with prostate cancer who were using no conventional treatments at the time (Ornish *et al.*, 2005). Also, women on low fat diet were found to have a markedly lower risk of breast cancer recurrence (Chlebowski *et al.*, 2006).

8.2. Medication:

The concept that medications could be used to prevent cancer is an attractive one, and many high-quality clinical trials support the use of such chemoprevention. Aspirin has been found to reduce the risk of death from cancer (Rothwell *et al.*, 2011). Daily use of tamoxifen or raloxifene has been demonstrated to reduce the risk of developing breast cancer in high-risk women by about 50% (Vogel *et al.*, 2006) .The effect of COX-2 inhibitors such as celecoxib upon the risk of colon polyps had been studied in familial adenomatous polyposis and in the general population (Bertagnolli *et al.*, 2006).

8.3. Vaccination:

Vaccines have been developed that prevent some infection by some viruses that are associated with cancer and stimulate an immune response against cancer-specific epitopes. Human papillomavirus vaccine decreases the risk of developing cervical cancer. The hepatitis B vaccine prevents infection with hepatitis B virus and thus decreases the risk of liver cancer (Irigaray *et al.*, 2007).

8.4. Screening:

Cancer screening involves efforts to detect cancer after it has formed, but before any symptoms appear. This may involve physical examination, blood or urine tests, or medical imaging. Cancer screening is not possible for some types of cancers, and even when tests are available, they are not recommended to everyone. Universal screening or mass screening involves screening everyone. Selective screening identifies people who are known to be at higher risk of developing cancer, such as people with a family history of cancer (Schiffman and Solomon, 2013).

8.5. Genetic testing:

Genetic testing for individuals at high-risk of certain cancers is recommended. Carriers of mutations may then undergo enhanced surveillance, chemoprevention, or preventative surgery to reduce their subsequent risk (Gulati and Domchek, 2008) .

9. Management of cancer:

Management of cancer depends upon the type of cancer, the location and grade of the tumor, and the stage of the disease, as well as the general state of a person's health. Many lines for management exist including: chemotherapy, radiation therapy, surgery, immunotherapy, monoclonal antibody therapy and other methods (Sleigh and Barton, 2010).

Complete removal of the cancer without damage to the rest of the body is the goal of treatment for most cancers. Sometimes, this can be accomplished by surgery, but the ability of cancers to invade adjacent tissue or to spread to distant sites by microscopic metastasis often limits its effectiveness. Surgery often required the removal of a wide surgical margin or a free margin. The effectiveness of chemotherapy is often limited by toxicity to other tissues in the body. Radiation can also cause damage to normal tissue (Hayden, 2009) .

Experimental cancer treatments are studied in clinical trials to compare the proposed treatment to the best existing treatment. They may be entirely new treatments, or they may be treatments that have been used successfully in one type of cancer and are now being tested to see whether they are effective in another type (Winther and Jorgensen, 2010) .

Alternative cancer treatments are treatments used by alternative medicine practitioners. These are a group of non-related interventions and include mind–body interventions, herbal preparations, massage, acupuncture, reiki, electrical stimulation devices and a variety of strict dietary regimens among others **(**Sleigh and Barton, 2010).

Many physicians are supportive of patients using alternative medicine in addition to standard management, especially for symptoms management, though certain types of alternative herbs or diets could actually interfere with treatments (Lawenda *et al.*, 2008)

In people who have metastatic disease when first diagnosed, oncologists should consider a palliative care consult immediately. Additionally, an oncologist should consider a palliative care consult in any patient they feel has a prognosis of less than 12 months even if continuing aggressive treatment (Brumley *et al.,* 2007).

10. Chemoprevention

There is increasing interest in strategies for cancer prevention due to the steady increase in global cancer incidence with its associated morbidity and mortality, together with the healthcare costs of treatment. One of these strategies is chemoprevention, which is defined as the use of natural, synthetic or biological agents to reverse, suppress or prevent either the initial phases of carcinogenesis or the progression of premalignant cells to invasive disease (Steward and Brown, 2013) . Interest in this area of research has markedly increased with improved understanding of the biology of carcinogenesis. Interest has been further stimulated by successes in the chemoprevention of breast, prostate and colon cancer. Over the last years, it has become apparent that the definition of chemoprevention should include the concept of 'delay', which means that the preventive effect may last for a definite period. The rate of tumor development is decreased even if the incidence eventually returns to that of the untreated population (Cai *et al.,* 2015) .

Chemoprevention may target a variety of steps in tumour initiation, promotion and progression (Mocanu *et al.,* 2015) . Many agents may have effects throughout the carcinogenic process. Compounds that inhibit cancer initiation are traditionally termed 'blocking agents'. They may prevent the interaction between chemical carcinogens or endogenous free radicals and DNA, thereby reducing the level of damage and resulting mutations which contribute not only to cancer initiation but also progressive genomic instability and overall neoplastic transformation (Ryan and Faupel-Badger, 2016).

Downregulation of chronic inflammatory responses and the production of reactive oxygen and nitrogen species may contribute to prevention of cancer initiation. Other protective processes include modulation of DNA methyl transferases to prevent or reverse the inactivation of tumor suppressor genes. Inhibition of histone deacetylases has also been described among a variety of effects of blocking agents on epigenetic mechanisms of carcinogenesis (West and Johnstone, 2014) .

Once initiation has occurred, chemopreventive agents may affect the promotion and progression of cancer cells. The major reported mechanisms contributing to this activity include inhibition of signal transduction pathways to inhibit the effects of tumor promoters which will lead to cell proliferation. In some cases, hormones may promote tumour progression, and anti-oestrogens such as tamoxifen can block this effect (Steward and Brown, 2013). Recent reports suggest interference with cancer cell metabolism and energy homoeostasis via effects on pathways such as AMP kinase may be an attractive goal for chemopreventive agents (Din *et al.,* 2012).

10.1. Types of chemoprevention:

Three broad approaches to the clinical use of chemopreventive agents have been described; primary, secondary and tertiary chemoprevention (Lee *et al.,* 2011). Primary chemoprevention means the administration of agents to the general healthy population or to those without obvious disease but with particular risk factors to modify carcinogen metabolism. Secondary chemoprevention involves the identification of individuals with premalignant lesions and administration of agents to prevent progression to invasive cancer (e.g. the use of non-steroidal anti- inflammatory drugs in patients with colorectal adenomas). Tertiary chemoprevention is defined as administration of agents to prevent recurrence in patients who have undergone successful treatment of early disease (Steward and Brown, 2013) .

10.2. Importance of Chemoprevention

The potential impact that chemoprevention could have on the death rate from cancer is evident from the way this approach has transformed the incidence of cardiovascular disease. The introduction of drugs that suppress cholesterol synthesis, modify platelet aggregation or lower blood pressure has led to a steady fall in heart disease over the past 3 decades. Chemoprevention can considerably reduce the morbidity and mortality rates of cancer and can reduce the total costs of treatment. It is essential to identify similar measurable risk factors for cancer that will allow chemoprevention to be focused on subgroups of individuals, reducing anxieties about potential side effects and reducing the risk of the disease (Kushi *et al.,* 2012; Steward and Brown, 2013).

10.3. Selection of Agents For Chemoprevention

There had been a major change in the guidelines for selection of chemopreventive agents in the last decade. Initially, selection was mainly based on observational studies reporting an association between consumption of pharmaceutical or dietary agents in a population, and a reduced incidence or mortality from cancer. Early-phase clinical studies should be performed to explore duration of dosing and biomarkers of efficacy but in the majority of cases (for example, for beta-carotene) large randomised trials were undertaken, exploring the relative rates of cancer over many years in exposed andcontrol populations (Naithani *et al.,* 2008).

In the recent years, the initial selection may still be based on epidemiological data suggesting an effect on cancer incidence, but subsequent extensive preclinical studies, using clinically achievable concentrations in models, which are relevant to human carcinogenesis, are increasingly undertaken before clinical trials begin (Scott *et al.,* 2009). Preclinical testing should comprise a series of investigations that must utilize the in vitro and in vivo mechanistic assays. These can include measures of the effect of the agent under investigation on potentially important processes, such as inhibition of proliferation, modification of angiogenesis and inflammation or induction of apoptosis. Subsequently, in vivo testing may explore the prevention of tumour development as measured by incidence, overall burden or time to occurrence. Historically, animal models involved carcinogenic exposure but, increasingly, transgenic/mutant rodent models are now utilised, given their greater relevance to the complexities of human carcinogenesis (Abate-Shen *et al*, 2008) . Such in vivo models can provide additional information on pharmacokinetics and safety. Target tissue levels can be measured to ensure appropriate delivery, and tissue concentrations producing an effect can be compared with subsequent human levels. This can provide a guide to appropriate dosing and schedule of treatment (Ryan and Faupel-Badger, 2016).

11. Cancer Chemotherapy

Chemotherapy is a category of cancer treatment that uses chemical substances to produce complete cure, prolong life or to reduce symptoms of cancer. Along with hormonal therapy and targeted therapy, it is one of the major categories of medical oncology. These are often used in conjunction with other cancer treatments, such as radiation therapy, surgery, and/or hyperthermia therapy. Chemotherapy is also used to treat other conditions such as amyloidosis, ankylosing spondylitis, multiplesclerosis, Crohn's disease, psoriasis, systemic lupus erythematosus, rheumatoid arthritis and sclerodema (Corrie and Pippa, 2008) .

Chemotherapy may use one drug at a time (single-agent chemotherapy) or several drugs at once (combination chemotherapy). The combination of chemotherapy and radiotherapy is chemoradiotherapy. Chemotherapy using drugs that convert to cytotoxic activity only upon light exposure is called photochemotherapy. There are many classifications for cancer chemotherapeutic agents. The most common one classify these agents according to their mechanism of action into alkylation agents, antimetabolites, antimicrotubules, topoisomerase inhibitors and cytotoxic antibiotics (Ricevuto *et al.,* 2010).

11.1. Alkylating Agents:

Alkylating agents are the oldest group of chemotherapeutics in use today, originally derived from mustard gas used in World War I (Corrie and Pippa, 2008) . They are so named because of their ability to alkylate many molecules, including proteins, RNA and DNA. This ability to bind covalently to DNA via their alkyl group is the primary cause for their anti-cancer effects. They may either bind twice to one strand of DNA (intrastrand crosslink) or may bind once to both strands (interstrand crosslink). If the cell tries to replicate crosslinked DNA during cell division or tries to repair it, the DNA strands can break leading to programmed cell death (Lind, 2008). Alkylating agents will work at any point in the cell cycle and thus are known as cell cycle- independent drugs. Their effect on the cells is dose dependent; the fraction of cells that die is directly proportional to the dose of drug. Alkylating agents include nitrogen mustards, nitrosoureas, tetrazines, aziridines, cisplatin and its derivatives. They impair cell function by forming covalent bonds with the amino, carboxyl, sulfhydryl and phosphate groups in biologically important molecules. Non-classical alkylating agents include procarbazine and hexamethylmelamine (Corrie and Pippa, 2008).

11.2. Antimetabolites:

Anti-metabolites are a group of molecules that inhibit DNA and RNA synthesis. Anti-metabolites resemble either nucleotides or nucleosides but have altered chemical groups (Parker, 2009) . These drugs exert their effect by either blocking the enzymes required for DNA synthesis or becoming incorporated into DNA or RNA. They prevent mitosis and produce DNA damage and programmed cell death (apoptosis). Unlike alkylating agents, anti-metabolites are cell cycle dependent. This means that they only work during a specific part of the cell cycle. Types of the anti-metabolites are the anti-folates, fluoropyrimidines, deoxynucleoside analogues and thiopurines (Lind, 2008) .

The anti-folates include methotrexate and pemetrexed. Methotrexate inhibits dihydrofolate reductase (DHFR) enzyme that regenerates tetrahydrofolate from dihydrofolate. When the enzyme is inhibited by methotrexate, the cellular levels of folate coenzymes diminish leading to inhibition of DNA synthesis and cell division (Tiwari, 2012) . Pemetrexed is another anti-metabolite that affects purine and pyrimidine production, and therefore also inhibits DNA synthesis. It primarily inhibits the enzyme thymidylate synthase, but also has effects on dihydrofolate reductase. The fluoropyrimidines include fluorouracil which is a nucleobase analogue that is metabolised in cells to form two active products; 5-fluourouridine monophosphate (FUMP) and 5-fluoro-2'-deoxyuridine 5'-phosphate (fdUMP) which inhibit thymidylate synthase enzyme

leading to cell death. The deoxynucleoside analogues include cytarabine, fludarabine, nelarabine, cladribine and pentostatin. The thiopurines include thioguanine and mercaptopurine (Parker, 2009).

11.3. Anti-Microtubule Agents:

Anti-microtubule agents are plant-derived chemicals that block cell division by preventing microtubule function. Microtubules are important cellular structures that are required for cell division (Lind, 2008). Vinca alkaloids and taxanes are the two main groups of anti- microtubule agents, and although both groups cause microtubule dysfunction, their mechanisms of action are completely opposite. The vinca alkaloids prevent the formation of the microtubules, whereas the taxanes prevent the microtubule disassembly. They prevent cancer cells from completing mitosis followed by arrest of the cell cycle which induces apoptosis. Moreover, these drugs can affect blood vessel growth that is essential for tumor growth and metastasis (Yue *et al.,* 2010).

Podophyllotoxin is an antineoplastic agent obtained primarily from the American Mayapple and Himalayan Mayapple. It has anti- microtubule activity and its mechanism is similar to that of vinca alkaloids in that they bind to tubulin, inhibiting microtubule formation. Podophyllotoxin is used to produce two other drugs with different mechanisms of action, namely etoposide and teniposide (Lv and Xu, 2011).

11.4. Topoisomerase Inhibitors:

Topoisomerase inhibitors are drugs that affect the activity of topoisomerase I and topoisomerase II. When the DNA double-strand helix is unwound, during DNA replication or transcription, for example, the adjacent unopened DNA winds tighter (supercoils), like opening the middle of a twisted rope. The stress caused by this effect is in part aided by the topoisomerase enzymes. They produce single- or double-strand breaks into DNA, reducing the tension in the DNA strand. This allows the normal unwinding of DNA to occur during replication or transcription. Inhibition of topoisomerase I or II interferes with both of these processes (Lind, 2008). Topoisomerase I inhibitors (irinotecan and topotecan) are derived from camptothecin, which is obtained from the Chinese ornamental tree Camptotheca acuminata. Drugs that target topoisomerase II can be divided into two groups. The topoisomerase II poisons prevent DNA replication and transcription, cause DNA strand breaks and lead to apoptosis. They include etoposide, doxorubicin and teniposide. The second group, catalytic inhibitors, blocks the activity of topoisomerase II, and therefore prevents DNA synthesis and translation. This group includes novobiocin, merbarone, and aclarubicin (Nitiss, 2009).

11.5. Cytotoxic Antibiotics:

The Cytotoxic antibiotics are a varied group of drugs that interrupt cell division. They include anthracyclines, actinomycin, bleomycin, plicamycin, and mitomycin. Doxorubicin and daunorubicin were the first two anthracyclines, and were obtained from the bacterium Streptomyces peucetius. Derivatives of these compounds include epirubicin and idarubicin (Tacar *et al.,* 2013) . Other clinically used drugs in the anthracyline group are pirarubicin, aclarubicin, and mitoxantrone. The mechanisms of anthracyclines include DNA intercalation, generation of highly reactive free radicals that damage intercellular molecules and topoisomerase inhibition. Actinomycin is a complex molecule that intercalates DNA and prevents RNA synthesis. Bleomycin, a glycopeptide isolated from Streptomyces verticillus that intercalates DNA and produces free radicals that damage DNA. Mitomycin is a cytotoxic antibiotic with the ability to alkylate DNA (Lind, 2008).

12. Natural agents and cancer therapy

Chemotherapy side effects depend mainly on the drugs and the doses the patient receives. The use of the traditional anticancer agents such as doxorubicin, 5-fluorouracil, methotrexate and cisplatin was faced by their dangerous adverse effects (El-Sayyad *et al.,* 2009). To decrease the dose and toxicity and increase the efficacy of chemotherapy regimens, various approaches were investigated. One of them was the search for natural agents with anticancer properties that can be used in combination with the traditional anticancer agents (Al-Harthi *et al.,* 2014).

The anticancer properties of plants have been recognized for centuries. Isolation of podophyllotoxin and several other compounds from the common may apple (Podophyllumpeltatum) ultimately led to the development of drugs used to treat testicular and small cell lung cancer (Sultana *et al.,* 2014). Many studies have focused on the chemoprotective properties of plants such as the effect of *Anacardium occidentale* in hepatoma, Asparagus racemosa in human epidermoid carcinoma, Boswelliaserrata in human epidermal carcinoma of the nasopharynx, Erthyrinasuberosa in sarcoma, Euphorbia hirta in Freund virus leukemia, Nigella sativa in lung carcinoma and Peaderiafoetida in human epidermoid carcinoma of the nasopharynx. Their anticancer effects were attributed to antioxidant and anti-inflammatory properties together with affection of the cell cycle and induction of the expression of tumor suppressor genes such as p53. They have the advantage of being nearly devoid of adverse effect which gives them a crucial role in cancer therapy (Mondal *et al.,* 2012) .

Cruciferous vegetables had been of specific interest for years in cancer therapy due to their high content of glucosinolates, whose major breakdown products (isothiocyanates and indoles) have anticarcinogenic properties in vitro and in vivo.

Most of the isothiocyanates are metabolized in vivo through the mercapturic acid pathway. Indole compounds can react with ascorbic acid producing ascorbigen and, at the low pH of the stomach, a series of condensed products that may act as further bioactive compounds (Bosetti *et al.*, 2012)**.**

They were suggested to inhibit cancer cell growth by interfering with the production of proteins involved in abnormal cellular reproduction and by promoting the production of tumour suppressor proteins. Also, they were reported to affect cell proliferation, signal transduction and induce apoptosis in cancer cells by interfering with the production of compounds that cancer ordinarily produces to resist apoptosis (Hu *et al.*, 2015) .

13.CONCLUSION:

It can be concluded that cancer is a diseases in which a group of cells displays uncontrolled growth and invasion that destroy adjacent tissues, and sometimes metastasize to other locations in the body. It is associated morbidity and mortality. The causes of cancer are due to genetics, and environmental factors such as; infections, diet lack of physical activity, and obesity, stress, tobacco, radiation, and environmental pollutants. Cancer symptoms are local, metastatic, and systemic symptoms. Some of these effects can include weight loss, poor appetite, cachexia, fatigue, excessive sweating, anemia, and other specific conditions. Chemotherapy uses to produce complete cure, prolong life or to reduce symptoms of cancer. Many of chemoprotective natural products are used with the traditional anticancer agents. So, the patients should be advised to take one of natural products while they are treated with chemotherapy to decrease its harmful effects.

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