CAUSES AND TREATMENT FOR COLON AND LUNG CANCER.

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Summary

Cancer (medical term: malignant neoplasm) is a class of diseases in which a group of cells display uncontrolled growth, invasion, and sometimes metastasis. Cancer is difficult to conquer in all living systems. Despite decades of work at the clinical and the research level, a cure for certain types of cancer is still years away and cancer incidence continues to grow. It is known however, that most cancers arise by an uncontrollable replication of cells that lose their ability to halt the normal management other genomic materials. As research develops, treatments are becoming more specific for different varieties of cancer. There has been significant progress in the development of targeted therapy drugs that act specifically on detectable molecular abnormalities in certain tumors, and which minimize damage to normal cells.
Colorectal cancer and Lung cancers are the leading cause of cancer death in both men and women, and its annual incidence and mortality rates have both risen over the past 25 years. This review summarizes the most frequent causes and treatments for colon and lung cancers.

Key words: Colorectal cancer, Lung cancer, Treatment.

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Introduction

Cancer (medical term: malignant neoplasm) is a class of diseases in which a group of cells display uncontrolled growth (division beyond the normal limits), invasion (intrusion on and destruction of adjacent tissues), and sometimes metastasis (spread to other locations in the body via lymph or blood). These three malignant properties of cancers differentiate them from benign tumors, which are self-limited, and do not invade or metastasize. Most cancers form a tumor but some, like leukemia, do not. Cancer affects people at all ages with the risk for most types increasing with age.[1]Cancer caused about 13% of all human deaths in 2007[2] and (7.6 million).[3]

Cancers are caused by abnormalities in the genetic material of the transformed cells. [4] Cancer cells continue to divide where other cells will wait for a specific signal to continue dividing. In addition cancer cells ignore the stop and go signals that maintain a proper balance in tissue growth, but also recruit adjacent blood vessel (angiogenesis) to bring nutrients into the area. Most cancers can be treated and some cured, depending on the specific type, location, and stage. Once diagnosed, cancer is usually treated with a combination of surgery, chemotherapy and radiotherapy. As research develops, treatments are becoming more specific for different varieties of cancer. There has been significant progress in the development of targeted therapy drugs that act specifically on detectable molecular abnormalities in certain tumors, and which minimize damage to normal cells.

In 2009, an estimated 1,479,350 people in the United States will be diagnosed with cancer, and 5,62,340 will die of cancer. [5] Estimates of the premature deaths that could have been avoided through screening vary from 3% to 35%, depending on a variety of assumptions. The prevalence of malignant cancers and cancer mortality are also on the increase. In light of the growing prevalence of cancer and its implications to modern health care, equal impetus is being paid by the scientific community to research on the disease. Furthermore, countries witness a variation in the prevalence of cancer cases as well as in the types of cancer that afflict upon their populations. These rate differences suggest underlying variations in genetic and environmental factors within these regions that possibly contribute to the onset and development of cancer. Beyond the potential for avoiding death, screening may reduce cancer morbidity since treatment for earlier-stage cancers is often less aggressive than that for more advanced-stage cancers. Several potential harms must be considered against any potential benefit of screening for cancer. [6]

Table showing Major Types of Cancer & Therapies

Major Cancers	Potential Therapies
Melanoma (skin)	Surgery
Breast	Chemotherapy
Kidney	Radiation
Colon	Biological Therapies
Glands)	Gene Therapy
Lymphomas (Lymph	Hormone-Blocking/Supplementing
Ovary	Other
Lung	Chemotherapy

Signs of Cancer [7]

Signs of cancer depend on the type and location of the tumor. With some cancers, there may not be any signs until the tumor is large. Common signs include:

–   Feeling very tired.

–   Weight loss and that occurs without knowing why

–   Fever, chills or night sweats, Cachexia (wasting)

–   Lack of hunger

–   Physical discomfort or pain, ulceration

–   Coughing, shortness of breath or chest pain

–   Diarrhea, constipation or blood in the stool,anemia

–   Tumor, hemorrhage, jaundice

–   Enlarged lymph nodes, cough and hemoptysis, hepatomegaly
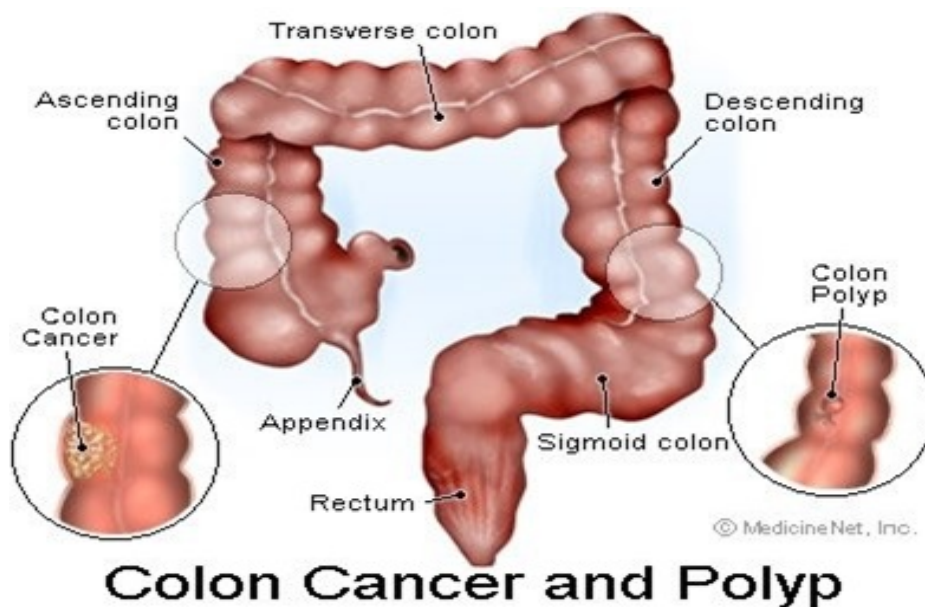
Causes of Cancer [8-16]

–   DNA Mutations

–   Non ionizing and ionizing Radiation

–   Other environmental factors (tobacco, alcohol, asbestos, etc)

–   Random somatic mutations

–   Inherited germ line mutations

–   Genetic predisposition-

–   Rb, p53, APC, CDKN2A, BRCA1, BRCA2

–   MHC incompatibility

–   Immune system disinfection.

–   Infectious agents

–   Viral

–   HPV – cervical cancer

–   Hepatitis – liver cancer

–   Vaccines have been developed and are extremely effective – not available

–   Bacterial

–   H. pylori – stomach cancer

Prevention [17]

The risk of cancer is reduced by:

–   Not smoking or using tobacco

–   Using sunscreen, hats and clothing to protect your skin when outside

–   Limiting the amount of alcohol as a drink

–   Limiting the amount of high fat foods, especially from animal sources

–   Eating plenty of fruits, vegetables and high fiber foods

–   Being physically active

–   Consulting doctor each year.

–   Cancer screenings may help find cancers at their early, most treatable stages.

1.   Colon Cancer

Colon Cancer and Polyp

        In Western societies, colon cancer is one of the major causes of cancer death. 110,000 new cases are diagnosed every year in the United States, and 55,000 people die annually because of this disease. There is a wide geographic variation in incidence, with a 20-fold variance worldwide. [18] Colorectal cancers are the third most common cancers in men and women.

Incidence of colorectal cancer is highest in developed countries such as the United States and Japan, and lowest in developing countries in Africa and Asia. According to the American Cancer Society, it is the third most common type of cancer in both men and women in the United States. Incidence is slightly higher in men than women, and is highest in African American men. The American Cancer Society estimates that about 147,000 cases of colorectal cancer are diagnosed and about 50,000 people die from the disease each year in the United States. The death rate from colon cancer has declined over the past 15 years due to improved screening methods and advances in treatment. This decrease probably reflects the decreasing trends in incidence rates and the increasing survival rates. [19, 20]

        Though it is recognized that genetic factors are important determinants for the genesis of colorectal cancer in individuals [21], it appears that differences in colon cancer incidence are mainly attributable to environmental factors.[22] Epidemiological studies have shown that especially people with a Western-style diet (high meat, high fat, low fiber) are at high risk for colon cancer. Incidence increases in countries with a high meat consumption. [23] More specifically, red meat, but not white meat, increases risk for colon cancer. [24, 25] Bile acids have been implicated as important etiological factors in colon cancer. [26, 27, 28, 29]

Risk Factors [30-36]

 A personal or family history of colorectal cancer or polyps, and inflammatory bowel disease has been associated with increased colorectal cancer risk. Other possible risk factors include lack of physical inactivity, high- fat and/or low- fiber diet, long term smoking, as well as inadequate intake of fruits and vegetables. Recent studies have suggested that estrogen replacement therapy and nonsteroidal anti-inflammatory drugs such as aspirin may reduce colorectal cancer risk.

Early Detection [37-39]

Beginning at age fifty, men and women should have one of the following: a fecal occult blood test (FOBT) and flexible sigmoidoscopy (if normal, repeat FOBT annually, and flexible sigmoidoscopy every five years), or colonoscopy (if normal, repeat every ten years), or double-contrast barium enema (if normal, repeat every five to ten years). A digital rectal examination should be done at the same time as sigmoidoscopy, colonoscopy, or double-contrast barium enema. These tests offer the best opportunity to detect colorectal cancer at an early stage when successful treatment is likely, and to prevent some cancers by detection and removal of polyps.People should begin colorectal cancer screening earlier and/or undergo screening more often if they have a personal history of colorectal cancer or adenomatous polyps, a strong family history of colorectal cancer or polyps, a personal history of chronic inflammatory bowel disease, or if they are a member of a family with hereditary colorectal cancer syndromes.

Signs and Symptoms: [3, 40]

Rectal bleeding, blood in the stool, a change in bowl habits and Others.

Treatment [3, 40]

Surgery is the most common form of therapy for colorectal cancer, and for cancers that have not spread, it is frequently curative. Chemotherapy, or chemotherapy plus radiation are given before or after surgery to most patients whose cancer has deeply perforated the bowel wall or has spread to the lymph nodes. A permanent colostomy (creation of an abdominal opening for elimination of body wastes) is seldom needed for colon cancer and is infrequently required for rectal cancer

DIFFERENT DRUGS USED IN COLON CANCER[40]

a) SYNTHETIC DRUGS

Drug	Mode of Action	Side Effect
Panitumumab	It is a recombinant, fully humanized IgG2 monoclonal antibody. It binds competitively tothe extra cellular domain of epidermal growth factor receptor (EGFR) on normal or tumour cells, and thus inhibits ligand-induced receptor autophosphorylation. EGFR activation leads to cell proliferation,differentiation, cell survival, angiogenesis, and invasion/metastases. The KRAS gene encodes a protein involved in signal transduction. Patients with mutated KRAS colorectal tumours do not appear to benefit from EGFR monoclonal antibody inhibitor therapy. It has demonstrated improvement in progression free survival.	Edema (12%) Hypertension (5%) Venous thromboembolism Anxiety, depression, insomnia (5%) Vertigo, dizziness, headache (4%) Parasthesia, dysgeusia (3%)
Capecitabine	It is a fluoro pyrimidine, which is converted into 5-fluoro uracil (5-FU) once inside the tumour. The drug takes advantage of the higher thymidine phosphorylase activity in malignant tissue. Its activity and safety had already been tested in two large phase III trials, where it proved to be superior to 5-FU/leucovorin. Both normal and tumor cells metabolize 5-FU to 5-fluoro-2'-deoxyuridine monophosphate (FdUMP) and 5-fluorouridine triphosphate (FUTP). These metabolites cause cell injury by two different mechanisms. First, FdUMP and the folate cofactor, N5-10 methylenetetrahydrofolate, bind to thymidylatesynthase (TS) to form a covalently bound ternary complex. This binding inhibits the formation ofthymidylate from 2'deoxyuridylate. Thymidylate is the necessary precursor of thymidinetriphosphate, which is essential	Diarrhea, nausea, vomiting, stomatitis (sores in mouth and throat), abdominal (stomach area) pain, upset stomach, constipation, Loss of appetite, and dehydration.

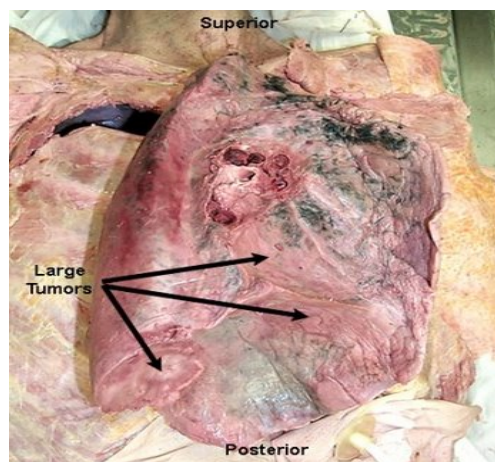| | for the synthesis of DNA, so that a deficiency of this compound can inhibit cell division. Second, nuclear transcriptional enzymes canmistakenly incorporate FUTP in place of uridine triphosphate(UTP) during the synthesis of RNA. This metabolic error can interfere with RNA processingand protein synthesis | |

Oxaliplatin	The exact mechanism of action of Oxaliplatin is not known. Oxaliplatin forms reactive platinum complexes, which are believed to inhibit DNA synthesis, by forming interstrand and intrastrand cross-linking of DNA molecules. Oxaliplatin is not generally cross resistant to cisplatin or carboplatin, possibly due to the DACH group and resistance to DNA mismatch repair. Preclinical studies have shown oxaliplatin to be synergistic with fluorouracil and SN-38, the active metabolite of irinotecan. Oxaliplatin is a radiationsensitizing agent. It is cell-cycle-phase nonspecific.	Anaphylaxis, Anemia, Febrile Neutropenia, Hemolytic Anemia, Neutropenia, thrombocytopenia, fever,Alopecia, Diarrhea, Mucositis,Nausea, Vomiting and Hepatic liver function Abnormalities.
Irinotecan	It is a semi synthetic analog of camptothecin characterized by the presence of a bulky piperidino side chain at the C-position which causes S-phase specific cell killing by poisoning Topo-I in the cell and exciting results from a randomized trial in combination with CDDP in patients with extensive small-cell lung cancer	Diarrhea, Dehydration Nausea and vomiting Abdominal pain , Dyspepsia/flatulence Constipation, hiccups Colitis, typhlitis, ileus, Obstruction, bleeding

| NSAID'S | The mechanisms by which NSAIDs act to reduce the risk of colon carcinogenesis is not yet clearly understood. Accumulating evidence points to inhibition of Arachidonic acid (AA) metabolism via COX enzymes, which, in turn, modulate the synthesis of prostaglandins (PGs) that affect cell proliferation, tumor growth, and immune responsiveness. NSAIDs prevent the formation of PGH2, the firstcommitted step in the metabolism of AA into a complex cascade of signaling lipids, such as PGD2, PGE2, PG I2, and thromboxane B2, the principal prostanoid metabolite in platelets. At low micromolar range therapeutic concentrations. NSAIDs are not known to influence other pathways of arachidonic acid metabolism

except indirectly by increasing the intracellular concentration of free AA, which potentially causes shunting of AA through other metabolic pathways such as lipoxygenase . | |

Table No-2 Synthetic Drugs Used in Colon Cancer.

2. **Lung Cancer**

Lung cancer is the leading cause of cancer death in both men and women, and its annual incidence and mortality rates have both risen over the past 25 years. Despite the fact that lung cancer is common and lethal, no screening strategy has been recommended to reduce the mortality. [41]

Lung cancer accounts for more deaths than any other malignancy in the world. Although surgery offers the best prospect of cure for patients with early stage tumors [42,43], the majority already have advanced to inoperable disease by the time they develop symptoms and present to their general practitioners. The five year survival rates for patients with lung cancer have remained depressively low at 7-13%. [44, 45]

Lung cancer is the most common cause of death due to cancer in both men and women throughout the world. The American Cancer Society estimates that 219,440 new cases of lung cancer in the U.S. will be diagnosed and 159,390 deaths due to lung cancer will occur in 2009. According to the U.S. National Cancer Institute, approximately one out of every 14 men and women in the U.S. will be diagnosed with cancer of the lung at some point in their lifetime. Lung cancer is predominantly a disease of the elderly; almost 70% of people diagnosed with lung cancer are over 65 years of age, while less than 3% of lung cancers occur in people under 45 years of age.

Signs and Symptoms:

Persistent cough, sputum streaked with blood, chest pain, and recurring pneumonia or bronchitis and other symptoms of cancer.

Risk Factors

Cigarette smoking is by far the most important risk factor in the development of lung cancer. Other risk factors include exposure to certain industrial substances, such as arsenic; some organic chemicals; radon and asbestos, particularly for persons who smoke; radiation exposure from occupational, medical, and environmental sources; air pollution; tuberculosis; and environmental tobacco smoke in nonsmokers.

Early Detection

Because symptoms often do not appear until the disease is advanced, early detection is difficult. In those who stop smoking when precancerous changes are found, damaged lung tissue often returns to normal. Chest x- ray, analysis of cells contained in sputum, Positron emission tomography (PET), Magnetic resonansce imaging (MRI), Blood tests and fiberoptic examination of the bronchial passages assist in diagnosis.

Treatment

Treatment options are determined by the type and stage of the cancer and include surgery, radiation therapy, and chemotherapy. For many localized cancers, surgery is usually the treatment of choice. Because the disease has usually spread by the time it is discovered, radiation therapy and chemotherapy are often needed in combination with surgery. Targeted therapy using erlotinib, Photodynamic therapy [PDT], Radiofrequency ablation [RFA] are also used now a day. [3]

DIFFERENT DRUGS USED IN LUNG CANCER [46]

a) SYNTHETIC DRUGS

Name of Drug	Mode of Action	Combination with another drug
Irinotecan	It is a semi synthetic analog of camptothecin characterized by the presence of a bulky piperidino side chain at the C-position which causes S-phase specific cell killing by poisoning Topo-I in the cell and exciting results from a randomized trial in combination with CDDP in patients with extensive small-cell lung cancer.	CisDiamminechlro platin (CDDP)
Dosetaxel	It is acts by disrupting the micro tubular network in cells that is essential for cell division. It promotes the assembly of tubulin into stable microtubules, while simultaneously inhibiting their disassembly. This leads to the production of microtubule bundles without normal function and to the stabilization of microtubules, resulting in the inhibition of mitosis in cells.	Platinum-based chemotherapy
Gemcitabin	It induces cell death is primarily by apoptosis, although the exact molecular events responsible for triggering are not known. The spectrum of activity of gemcitabine in solid tumors is related to specific characteristics. Compared with other nucleoside analogues, It serves as better transporter substrate for membrane pumps, is phosphorylated more efficiently, and is eliminated more slowly, favoring a longer retention time of the active form in tumor cells.	CisDiamminechlro platim (CDDP)

Conclusion

Cancer is the most dreadful disease causing invasion and metastasis to the body and hence, it is difficult to conquer in all living systems. Despite decades of work at the clinical and the research level, a cure for certain types of cancer is still years away and cancer incidence continues to grow. There are millions of patients all over the world who requires the awareness and basic knowledge about the colon and lung cancer and its effective treatment.

Our review is aimed to highlight the Causes and treatments of chronic cancer and also attempts to give the remedy for effective treatment of Cancer. The Facts suggests that there is an enormous scope for the diagnosis, treatment and new drug discovery process.

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