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## **Cancer and Its Root Causes - A Historical Analysis**

*Mokshi Sharma*

*Assistant professor, Department of Zoology, Dev Samaj College for Women,  
Ferozpur City, Punjab, India.*

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### **Abstract**

*Cancer is the second leading cause of death in the world after cardiovascular diseases. Half of 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. Cancer is not a new disease and has afflicted people throughout the world. The word cancer came from a Greek words karkinos 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 the cancer, only palliative treatment. Communicating the status of the evolving science in the context of the overall scientific evidence base, and evidence-based dietary recommendations for cancer prevention, should be emphasized in guidance for the public and for individual patients. According to inscriptions, surface tumors were surgically removed in a similar manner as they are removed today. A historical view of the discoveries of the causes and treatment of human cancer is presented with extended discussions of the difficulties encountered in identifying viral causes of cancer.*

*Keywords: Infections, Causes, Cancer, Carcinogens, Historical, treatments*

### **Introduction**

Cancer is the second leading cause of death in the world after cardiovascular diseases. Half of men and one third of women in the United States will develop cancer during their lifetimes. The question of “what causes cancer” has intrigued people for generations. 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<sup>1</sup>. Today, millions of cancer people extend their life due to early identification and treatment. Cancer is not a new disease and has afflicted people throughout the world<sup>1,2</sup>. The word cancer came from a Greek words karkinos to describe carcinoma tumors by a physician Hippocrates (460–370 B.C), but he was not the first to discover this disease. It was learned that people who migrated to other countries, developed types of cancer common to their adopted countries, rather than their homelands. This implied that most cancers were caused by exposures in the environment, rather than inherited genetic factors. 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<sup>2,3,4</sup>. Some of the earliest evidence of human bone cancer was found in mummies in ancient Egypt and in ancient manuscripts dates

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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 the cancer, only palliative treatment<sup>3,4,5</sup>. According to reports, surface tumors were surgically removed by same method as they are removed today<sup>4,5</sup>.

### **Cancer and its Cause**

Cancer develops when the normal cells of the body in a particular part begin to grow out of control. There are different types of cancers; all types of cancer cells continue to grow, divide and re-divide instead of dying and form new abnormal cells. Through blood circulation or lymph vessels some types of cancer cells often travel to other parts of the body (metastasis), where they begin to grow. Most of the time when ever DNA was damaged, the body is able to repair it, unfortunately in cancer cells, damaged DNA is not repaired. Many times though, a person's DNA becomes damaged by exposure to something in the environment, like smoking. Cancer generally forms as a solid tumor<sup>5</sup>. Some cancers like leukemia (blood cancer) do not form tumors. Instead, leukemia cells involve the blood and blood forming organs and circulate through other tissues where they grow.

Not all tumors are cancerous, some tumors are benign (non-cancerous). Benign tumors do not grow and are not life threatening. Different types of cancer cells can behave differently. The risk of developing many types of cancers can be reduced by changes in lifestyle by quitting smoking and eating low fat diet. If cancer is identified in early stage it is easy to treat and may have better chances for living many years<sup>5,6</sup>. For example when a breast cancer cell spread to liver through blood circulation, the cancer is still called as breast cancer, not a liver cancer. Due to damage of DNA cancer cells develop from normal cells.

### **Old Theories about Cancer**

**Humoral theory** – In Greek, *carcinus* refers to the familiar zodiac sign Cancer, the Crab. The Greeks applied the term “crab” to the disease because of the tendril-like projections, which resemble the ten-legged sea creature. In modern medicine, a carcinoma (arising from epithelial cells) is the most common type of cancer, the other types being sarcoma (from connective tissue), lymphoma (from blood cells), germ cell tumors (from totipotent, or reproductive, cells), and blastic tumors (from immature tissue) <sup>6</sup>. Hippocrates believed that the body contained 4 humors (body fluids), (a) blood, (b) phlegm, (c) yellow bile and (d) black bile. The cause of cancer was imbalance of these fluids which result in disease and excess of black bile in a particular organ site. 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.

**Lymph theory** – In this theory states that cancer formation was by fluid called lymph. Life was believed to consist of continuous movement of the fluids like as blood and lymph in the body. The lymph theory was supported in 17th century that tumors grow from lymph constantly thrown out by the blood. Further theories preceding the invention of the modern microscope include the “lymph theory” of cancer<sup>6</sup>. Hippocrates' humoral theory was replaced first by this theory. The lymph theory purported in the early eighteenth century that cancer formed because of fermenting and degenerating lymphatic fluid. John Hunter,

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the Scottish surgeon who anticipated the advent of oncological surgery, supported the lymph theory.

**Parasite theory**—Till 18th century, scientists believed that cancer was contagious and spreads through parasite. The “parasite theory” comes in the seventeenth and eighteenth centuries. This theory alleged that cancer was an infectious disease that relied upon the transmission of an invisible contagion<sup>6</sup>. The parasite theory persisted off and on until the twentieth century. In 1926 an oncological scientist named Johannes Fibiger earned a Nobel Prize for research erroneously finding that certain worms caused stomach cancer. Later, other scientists disproved this theory.

**Blastema theory**—Cancer is not with lymph but made up of cells in 1838 by Muller. His student, Virchow (1821-1902) determined that all cells including cancer cells were derived from other cells. More modern, scientifically sound theories replaced these previous theories. One such theory was the “blastema theory.” The German pathologist Johannes Müller (1801-1858), who mentored Rudolph Virchow, developed the blastema theory in 1838. The blastema theory postulated that cancer was made up of cells and not lymphatic fluid and that cancer cells arose from budding elements (called blastema) between normal tissues. Virchow demonstrated that cancer spread like liquid through chronic irritation of tissues<sup>6,7</sup>. German surgeon Karl Thiersch (1822-1895) proved that cancers metastasize through the spread of malignant cells, not liquid. Developed in the end of the nineteenth century and lasting through the 1920s, a further theory developed that hypothesized that cancer was caused by trauma or injury. The theory is rejected by Scientists because the experiment to induce cancer on laboratory animals through injury is failed. All of these theories eventually faltered, but they paved the way for scientific advances to come.<sup>6</sup>

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

**Trauma theory**—Despite advances in the understanding of cancer, from the late 1800s until the 1920s, trauma was thought by some to cause cancer. This belief was maintained despite the failure of injury to cause cancer in experimental animals<sup>4,5</sup>.

**Discovery of Oncogenes and Tumor Suppressor Genes**—By the middle of the 20<sup>th</sup> century, scientists began solving the complex problems of chemistry and biology behind cancer. Watson and Crick were received Nobel Prize in 1962 for the discovery of DNA helical structure. Mutations could cause damaged to genes and scientist learned how genes were worked. Scientists proved that cancer could be caused by chemicals (carcinogens), radiation, viruses and also inherited from ancestors. Most carcinogens were damage the DNA, which led to abnormal growth of cells<sup>6,7,8</sup>. Normal cells with damaged DNA die but in case of cancer cells with damaged DNA do not die. During the 1970s, scientists discovered 2 important families of genes.

**Oncogenes**— These genes that cause normal cells to grow out of control and become cancer cells. The proto oncogenes are formed by the mutations of certain normal genes of the cell

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called (genes that normally control how often a cell divides and the degree to which it differentiates<sup>7,8</sup>).

**A tumor suppressor gene**—These are normal genes that control cell division, DNA repair and inform cells when to die. Cancer can be caused when a tumor suppressor gene doesn't work properly; growth of the cell is out of control. Oncogenes and tumor suppressor genes that are damaged by chemicals or radiation became cancerous. For example, the discovery of breast cancers genes BRCA1 and BRCA2. Other genes have been discovered that are associated with cancers that run in families, such as thyroid, pancreas, rectum, colon, kidney, ovary and skin cancers. as spontaneous cancers are more common than inherited cancers, accounting for less than fifteen percent of all cancers, it is important to understand these cancers because continued genetic research may enable scientists to identify all persons at high risk, which in turn promotes prevention and early intervention <sup>6,7,8</sup>.

### **Cancer screening and early detection**

In people who do not have any symptoms screening refers to tests and exams used to find a disease, such as cancer. The first screening test to be widely used for cancer was the Pap test. The test was developed by George Papanicolaou as a research method in understanding the menstrual cycle. In 1923, Papanicolaou presented his findings related to cervical cancer . At first, most doctors were skeptical, and it was not until the American Cancer Society (ACS) promoted the test during the early 1960s that this test became widely used <sup>4,5,7</sup>.

The first cancer screening test to be widely used was the Pap test. The test was first developed by George Papanicolaou as a method in understanding the menstrual cycle. He also identified Pap tests potential for early detection of cervical cancer. In 1960s mammography was developed for identification of breast cancer. Early detection of cervix, breast, colon, rectum, endometrium, prostate, thyroid, oral cavity, skin, lymph nodes, testes, and ovaries cancers were identified and practiced in the clinic <sup>5,6</sup>.

### **Cancer Treatment Methods**

#### **Surgery and use of modern technology**

Ancient physicians and surgeons knew that cancer can be come back after it was surgically removed. The Roman physician Celsus wrote, "After excision, even when a scar has formed, none the less the disease has returned." Galen was a 2nd-century Greek doctor whose books were preserved for centuries. He was thought to be the highest medical authority for over a thousand years. Galen viewed cancer much as Hippocrates had, and considered the patient incurable after a diagnosis of cancer had been made <sup>4,8,9</sup>. His views set the pattern for cancer management for centuries. After anesthesia was invented in 1846, surgeons Bilroth, Handley and Halsted led cancer operations by removing entire tumor together with lymph nodes. Later Paget a surgeon explained the term metastasis that cancer cells were spread from primary tumor to other places through the blood stream. Understanding the mechanism(s) of cancer spreading became a key element in recognizing the limitations of cancer surgery. In 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<sup>8,9,10</sup>.

Surgeons can operate using special surgical instruments through narrow tubes put into small cuts in the skin. These instruments can be used to look and work inside the abdomen (laparoscopic surgery) or chest (thoroscopic surgery). A similar instrument, the endoscope, can be used to remove some tumors in the colon, esophagus, or bladder by entering through natural body openings such as the mouth or anus. Recently, less invasive ways of destroying tumors without removing them are being studied including liquid nitrogen spray to freeze and kill cancer cells (cryosurgery).<sup>11,12</sup> Lasers also can be used to cut the tumor tissue of cervix, larynx, liver, rectum, skin and other organs. Radiofrequency ablation transmits radio waves to a small antenna placed in the tumor to kill cancer cells by heating them<sup>13,14</sup>.

### **Hormone Therapy**

The groundwork for an important modern method to treat and prevent breast cancer comes in picture in 19th century. In 1878 Thomas Batson 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<sup>13,14</sup>. Now new classes of drugs (aromatase inhibitors, LHRH analogs) are being used to treat prostate and breast cancers. The big question in mind of all the scientist that how hormones influence growth of cancer has guided progress in developing as well as reducing the risk of breast and prostate cancers<sup>15,16,17</sup>.

### **Radiation therapy**

In 1896 Roentgen discovered "X-ray" and after 3 years from discovery the X-ray 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: (a) conformal proton beam therapy (proton beam will be used for killing tumor cells instead of X-rays); (b) stereotactic surgery and stereotactic therapy (gamma knife can be used to deliver and treat common brain tumor); (c) intra-operative radiation therapy (cancer has been removed surgically followed by radiation to the adjacent tissues)<sup>17</sup>.

### **Adjuvant therapy**

Adjuvant therapy also known as **adjunct therapy, add-on therapy, and adjuvant care**, is therapy that is given in addition to the primary or initial therapy to maximize its effectiveness. It is the use of chemotherapy after surgery to destroy the few remaining cancer cells in the body<sup>18</sup>. It adjuvant therapy actually modified the effect of others. Adjuvant therapy was used in colon and testis cancers.

### **Immunotherapy**

Use of biological agents that mimic some of the natural signals that body uses to control tumor growth is called immunotherapy. We can produce these natural biological agents in the laboratory including interferons, interleukins, cytokines, endogenous angioinhibitors and antigens. These agents are given to patients to imitate or influence the natural immune response<sup>16,17</sup>. In 1990s scientists produced therapeutic monoclonal antibodies rituximab and

trastuzumab that specifically targeted lymphoma and breast cancer cells. Cancer immunotherapy is a therapy used to treat cancer patients that involves or uses components of the immune system. Some cancer immunotherapies consist of antibodies that bind to, and inhibit the function of, proteins expressed by cancer cells. Other cancer immunotherapies include vaccines and T cell infusions. At present scientists are developing vaccines to boost the body's immune response against cancer cells. It represents an important step forward in cancer treatment<sup>17,18</sup>.

### **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 X-rays after 50 years of anesthesia was discovered. Later doctors identified that nitrogen mustard can kill rapidly proliferating lymphoma cancer cells. Chemotherapy is one of the major categories of the medical discipline specifically devoted to pharmacotherapy for cancer, which is called *medical oncology*. Over the years, many chemotherapy drugs are used and resulted in the successful treatment of many types of cancers<sup>4,12</sup>. Now new approaches are being studied to reduce the side effects of chemotherapy including use of, (a) new combinations of drugs, (b) liposomal and monoclonal antibody therapy to target specifically cancer cells, (c) chemo protective agents to reduce chemotherapy side effects, (d) hematopoietic stem cell transplantation and (e) agents that overcome multidrug resistance<sup>15,17</sup>.

### **Targeted Cancer Treatments**

Most of the drugs used in cancer therapy worked by killing cancer cells in 1990s. Unfortunately chemotherapy agents used, also killed some normal cells and had a greater effect on cancer cells. Targeted therapies work by influencing the processes that control growth, division, and spread of cancer cells, as well as the signals that cause cancer cells to die naturally (the way normal cells do when they are damaged or old).

### **Growth signal inhibitors**

Growth factors are responsible for growth and division of the cell. Around 1960s growth factors role in fetal growth and tissue repair was recognized and later scientists realized that abnormal levels of growth factors contribute to the growth of cancer cells. The change in growth factors signaling leads to abnormal behavior of cancer cells. Present targeted therapies that block growth factor signals are trastuzumab, gefitinib, imatinib and cetuximab. Through the Middle Ages for over 1,300 years. During this period, the study of the body, including autopsies, was prohibited for religious reasons, which limited progress of medical knowledge<sup>12,18</sup>.

### **Drugs that induce apoptosis**

Apoptosis is a natural process through which cellular DNA gets damaged and cells ultimately will die whereas apoptosis induced drugs can force cancer cells to die without DNA repair. The fact that disparate agents, which interact with different targets, induce cell death with some common features (endonucleolytic cleavage of DNA, changes in

chromatin condensation) suggests that cytotoxicity is determined by the ability of the cell to engage this so-called 'programmed' cell death.

### **Endogenous angioinhibitors**

Angiogenesis is the formation of new blood vessels from existing vessel. Normally angiogenesis is a healthy process, that help the body to heal wounds and repair damaged body tissues, whereas in cancerous condition this process supports new blood vessel formation that provide a tumor with its own blood supply and nutrients. Angioinhibition is a form of targeted therapy that uses drugs to stop tumors from making new blood vessels<sup>16,17,18</sup>. This concept was first proposed by Judah Folkman from Harvard Medical School, but it wasn't until 2004 that the first angioinhibitor bevacizumab was approved for clinical use. At present there are about 25 endogenous angioinhibitors in clinical trials and many more in preclinical studies for the treatment of cancer. There are two general categories of angioinhibitors: (i) antibodies or small molecules that target pro-angiogenic factors of tumor cells such as VEGF, bFGF or PDGF, and (ii) endogenous angioinhibitors such as thrombospondin-1, angiostatin, interferons, endostatin, arretsen, canstatin and tumstatin that inhibit angiogenesis by targeting vascular endothelial cells. We have discovered several angioinhibitors signaling mechanisms and their significance for the treatment of cancer<sup>17,18</sup>.

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