Published in final edited form as:
J Cancer Sci Ther. 2009 December 1; 1(2): 1–4. doi:10.4172/1948-5956.100000e2.

History of Cancer, Ancient and Modern Treatment Methods

Akulapalli Sudhakar[1,2,3]

[1] Cell Signaling and Tumor Angiogenesis Laboratory, Department of Genetics, Boys Town National Research Hospital, Omaha, NE 68131, USA

[2] Department of Biomedical Sciences, Creighton University School of Medicine, Omaha, NE 68131, USA

[3] Department of Biochemistry and Molecular Biology, University of Nebraska Medical Center, Omaha, NE 68198, USA

History of Cancer

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. According to inscriptions, surface tumors were surgically removed in a similar manner as they are removed today.

What is Cancer? and Cause of Cancer

Cancer develops when normal cells in a particular part of the body 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. Some types of cancer cells often travel to other parts of the body through blood circulation or lymph vessels (metastasis), where they begin to grow. 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. Generally cancer cells develop from normal cells due to damage of DNA. 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. People can also inherit damaged DNA from parents, which accounts for inherited cancers. 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. Some cancers like leukemia (blood cancer) do not form tumors. Instead, leukemia cells involve the blood and blood forming organs and circulate

*Corresponding author: Dr. Sudhakar Akulapalli, Assistant Professor/Staff Scientist II, Creighton University School of Medicine and University of Nebraska Medical Center, Director & Coordinator: Cell Signaling and Tumor Angiogenesis Laboratory, Boys Town National Research Hospital, 555 N, 30th Street, Omaha NE 68131 USA, Tel: # (402) 498-6681; Fax: (402) 498-6331; akulapallis@boystown.org.

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.

Old Theories about Cancer

Humoral theory—Hippocrates believed that the body contained 4 humors (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.

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 as blood and lymph in the body. The lymph theory was supported in 17^{th} century that tumors grow from lymph constantly thrown out by the blood.

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.

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.

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

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

Discovery of Oncogenes and Tumor Suppressor Genes—By the middle of the 20th 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. Later scientists learned how genes were worked and how they could be damaged by mutations. Scientists identified 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. Cancer cells with damaged DNA do not die, where as normal cells with damaged DNA 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. They are formed by the mutations of certain normal genes of the cell called protooncogenes (genes that normally control how often a cell divides and the degree to which it differentiates).

Tumor suppressor genes—These are normal genes that control cell division, DNA repair and inform cells when to die. When a tumor suppressor gene doesn't work properly, cells can grow out of control, which can lead to cancer. Scientists identified oncogenes and tumor suppressor genes that are damaged by chemicals or radiation. 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.

Modern Carcinogens

In 1911 Peyton Rou was discovered a type of cancer in chickens that was caused by Rous sarcoma virus. In 1915, cancer was induced for the first time in rabbits by coal tar applied to skin. 150 years had passed since the most destructive source of chemical carcinogens known to man, tobacco (nicotin) was rediscovered as a carcinogen. As of today more than 100 carcinogens (chemical, physical, and biological) were identified. From many of these carcinogens associations recognized long before, scientists understood the mechanism by which the cancer was produced. The continuing research is discovering new carcinogens, explaining how they cause cancer and providing insight into ways to prevent it.

Cancer causing viruses

(1) Hepatitis B or C viruses cause liver cancer. (2) Epstein-Barr viruses cause non-Hodgkin lymphomas and nasopharyngeal cancer. (3) The human immunodeficiency virus (HIV) is associated with Kaposi Sarcoma and non-Hodgkin lymphoma. (4) Human papilloma viruses (HPVs) are associated with cervix, vulva and penis cancers.

Cancer screening and early detection

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. Later 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.

Cancer Treatment Methods

Surgery and use of 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 to consult a doctor in early stage. 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 reported that cancer cells were spread from primary tumor to other places through the blood stream (metastasis). 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. Recently, less invasive ways of destroying tumors without removing them are being studied including liquid nitrogen spray to freeze and kill cancer cells (cryosurgery). Lasers also can be used to cut the tumor tissue of cervix, larynx, liver, rectum, skin and other organs.

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. Over the years, use of many chemotherapy

drugs has resulted in the successful treatment of many types of cancers. 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) chemoprotective agents to reduce chemotherapy side effects, (d) hematopoietic stem cell transplantation and (e) agents that overcome multidrug resistance.

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.

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: (a) c*onformal 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).

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.

Immunotherapy

Use of biological agents that mimic some of the natural signals that 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 angioinhibitors and antigens. In 1990s scientists produced therapeutic monoclonal antibodies rituximab and trastuzumab that specifically targeted lymphoma and breast cancer cells. At present scientists are developing vaccines to boost the body’s immune response against cancer cells.

Targeted Cancer Treatments

Until 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.

Growth signal inhibitors

Growth factors will inform cells when to grow and divide. 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. During 1980’s scientists recognized that changes 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.

Drugs that induce apoptosis

Apoptosis is a natural process through which cellular DNA gets damaged and cells ultimately will die where as apoptosis induced drugs can force cancer cells to die without DNA repair.

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, nutrients and allow it to grow. Angioinhibition is a form of targeted therapy that uses drugs to stop tumors from making new blood vessels. This concept was first proposed by Judah Folkman from Harvard Medical School, but it wasn't until 2004 that the first angioinhibitor bevicizumab 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 thrombopondin-1, angiostatin, interferons, endostatin, arresten, 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.

Future Cancer Treatments

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.

Antiangiogenic chemotherapy

Recently, in many clinical trails angioinhibitors were also being used in combination with conventional chemotherapy. Clinical trails generally combine very low-dose of chemotherapy followed by angioinhibitor therapy. Combination of angioinhibitors will need to be tested vigorously in the future, as single angioinhibitors are approved for use of cancer. For example, it is very important to know whether bisphosphonates are synergistic with certain natural angioinhibitors such as angiostatin, endostatin, thrombospondin, arresten, canstatin tumstatin etc. Preventive angioinhibitory therapy may also be possible in the future, because angioinhibitory therapy is generally less toxic and less susceptible to induction of acquired drug resistance. Recently, some reports suggested that some foods have angioinhibitory substances. It is also better to test food that has high levels of natural angioinhibitors for prevention of cancer.

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.

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.

RNA expression profiling and proteomics

RNA expression profiling permits scientists to determine relative amounts of numerous RNA molecules at one time. Knowing what proteins or RNA molecules are present in cancer cell

can tell lot about how a cell is behaving and often can help to predict which drugs that particular tumor cell is likely to respond.

Finally winning the war against human cancer has been the focal point of present medical research. Single “cure-all” drug for cancer has not yet been developed, even though many new cancer treatment methods and drug targets have been discovered. More research studies and different clinical trails are the key to find a cure for cancer. The complexity of cancer disease requires scientific battle to fight against cancer in all frontiers.

Necessary of many open access cancer journals

Many popular cancer journals require payment for downloading research articles. Open access journals are freely available without subscription fee via the internet for immediate worldwide access to the full text of articles serving the best interests of the international research community without financial, legal, or technical barriers. Journal of Cancer Science & Therapy (JCST)), is an open-access and peer-reviewed international journal, recently created in response to the NIH Public Access Policy, in addition JCST using online manuscript submission, review and tracking systems of Editorial Manager® for quality and quick review processing.

At every stage of cancer research and development, quality of open access literature is integral to success. JCST is an Open Access journal that provides comprehensive scientific capabilities, and state-of-the-art technical reports to bring outstanding cancer R&D support.

Advances in global internet communication, and quality research reports under Open Access publication provide rapid scientific review of reports/research articles to consistently meet the requirements of human health.

The Main objective of JCST is to translate scientific and behavioral research into relevant cancer therapeutics development, strategic planning, sharing exchanging best practices under Open Access platform, and implementing effective cancer therapy requirements.

Acknowledgments

This work was supported by Flight Attendant Medical Research Institute Young Clinical Scientist Award Grant (#062558), Dobleman Head and Neck Cancer Institute Grant (#61905) and #RO1CA143128, startup funds of Cell Signaling and Tumor genesis Laboratory at Boys Town National Research Hospital to AS.

References

1. Angiogenesis inhibitors from Wikipedia, the free encyclopedia.
2. Angiogenesis Inhibitors Therapy: National Cancer Institute. A fact sheet that describes the process of eliminating the blood supply to tumors. Web site accessed at: www.cancer.gov/clinicaltrials/digestpage/angiogenesis-inhibitors
3. Contran, R.; Kumar, V.; Robbins, S. Pathologic Basis of Disease. 4. 1989.
4. Diamandopoulus GT. Cancer. An historical perspective. Anticancer Res 1996;16:1595–1602.
5. Kufe, DW.; Pollock, RE.; Weichselbaum, RR.; Bast, RC., Jr; Gansler, TS. Cancer Medicine. Decker Inc; 2003.
6. Encyclopedia Britannica. See entries on Medicine, History of Cancer.
7. Gallucci BB. Selected concepts of cancer as a disease. From the Greeks to 1900. Oncol Nurs Forum 1985;12:67–71. [PubMed: 3892501]
8. Kalluri R. Basement membranes: structure, assembly and role in tumour angiogenesis. Nat Rev Cancer 2003;3:422–433. [PubMed: 12778132]
9. Kardinal C, Yarbro JA. Conceptual history of cancer. Semin Oncol 1979;6:396–408. [PubMed: 394325]

10. Lyons, AS.; Petrucelli, RJ. Medicine: An Illustrated History. New York: Harry N. Abrams Publishers; 1978.
11. Progress against cancer. 2009. Web site accessed at: http://www.cancer.net/patient/Advocacy%20and%20Policy/Treatment_Advances_Timeline.pdf
12. Shimkin, MB. For sale by the Superintendent of Documents. U.S. Printing Office; Washington D.C: 1976. Contrary to Nature: Cancer; p. 20401DHEW Publication No (NIH) 76–720
13. Sudhakar A, Boosani CS. Signaling mechanisms of endogenous angiogenesis inhibitors derived from type IV collagen. Gene Regulation and System Biology 2007;1:217–226.
14. Sudhakar A, Boosani CS. Inhibition of tumor angiogenesis by tumstatin: insights into signaling mechanisms and implications in cancer regression. Pharm Res 2008;25:2731–2739. [PubMed: 18551250]
15. Sudhakar A. The matrix reloaded: new insights from type IV collagen derived endogenous angiogenesis inhibitors and their mechanism of action. J Bioequiv Availab 2009;1:52–62.
16. The history of cancer. 2009. Web site accessed at: http://www.bordet.be/en/presentation/history/cancer_e/cancer1.htm
17. Timeline: Milestones in cancer treatment. CureToday. 2009. Web site accessed at: http://www.curetoday.com/index.cfm/fuseaction/article.show/id/2/article_id/631
18. Halsted WS, Young HH, Clark JG. Early contributions to the surgery of cancer. Johns Hopkins Med J 1974;135:399–417. [PubMed: 4613916]