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Review Article

Cancer: From Theory to Practice –Ideology of Etiology and Treatment

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Abstract

Cancer is the second leading cause of death globally. About 277 different types of cancer are present. It occurs due to un-controlled division of cells. In women and men, most commonly found cancers are breast and prostate cancer, respectively. While in children, blood cancer is common. UV-Radiations, carcinogens, smoking, Alcohal are the main factors that increase the risk of cancer attack. Many evidences are found that this disease were also present in ancient mummies of Egypt. Many treatments are present that is useful for treating cancer. Researchers and oncologists reported that daily exercise and stopping cigarette is best for reducing the risk of cancer.

Keywords: Cancer; Lethal Disease; Immunotherapy

Abbreviations

MRI: Magnetic Resonance Imaging; KIR: Killer-cell Immunoglobulin-like Receptor; CRISPR: Clustered Regularly Interspaced Palindromic Repeats; UV: Ultra-voilet; HPV: Human Pappilloma Virus.

Introduction

Cancer is the second largest disease that causes more death, cardiovascular disease is the first one [1]. The word cancer comes from "Karkinos" by a physician name Hippocrates (460-370 BC). Some evidences are present that people of ancient Egypt also know about this disease. Researcher noticed that this disease also found in the mummies that are present in ancient Egypt [2]. First breast cancer was reported in 1500 BC and that treatment are present for this disease. Surgeons of that time remove that part by surgery. Cancer is produced in a body when body cells divide continuously and no cell death occur.

As we know that millions of cells are present in our body and these cells are divide in a controlled environment sometimes this controlled manner are disturb and cell division start continuously resulting in the formation of abnormal cell. These abnormal cells called cancer cells. These cancer cells unite and form a complex structure of tissues called tumor [1]. In our body DNA is present that code for protein. When DNA is damaged then different repair pathways present that repaired the damaged DNA. Sometimes damaged DNA cannot be repair and this unrepaired damage DNA causes cancer. If a cancer is present in family (2-3 person) then it means that cancer may be hereditary and this type of cancer has ability to transfer to the next generation [1-3]. Researcher also shows that metastatic tumor are due to the high level of mRNA [4]. When cancer is formed then it is transferred all over the body through blood circulation [5]. Some forms of cancer also present that cannot be transferred to other parts of body e.g. Benign Tumor [6].

Table 1: Comparison between two different cancer groups.

Benign Tumor	Malignant Tumor
Small	Large
Well differentiate	Poorly differentiate
Uniform size and shape	Size and shape not uniform
Few Mitosis	Multipolar Mitosis
Take stain Normally	Hyperchromatic nuclei
Non Invasive	Invasive
Islet cell Adenoma	Islet cell carcinoma
Stay localized	Metastasized
Squamous cell Papilloma	Squamous cell carcinoma

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In Asia, high number of Hepatitis B, C, HPV and Epstein Barr virus present that increase the chances of cancer [7]. Researcher not able to identify the specific reason of cancer and diagnosis of cancer is also a challenging for us [8,9]. Approximately 1.6 million people affected by cancer in 2014. 0.58 Million people died due to this disease only in USA [9]. Cancer have many types and the diagnose of specific type of cancer is a big challenge for human [8,10]. In men, commonly Lung, Prostate, Bronchus and Urinary Bladder cancer are found. While in women, Breast, Uterine and thyroid type cancer are in high amount [11]. So, according to data, we say that prostate cancer is common in men and Breast cancer is common in women [11]. In children, blood cancer and brain cancer are two types that diagnose mostly [12,13]. We able to remove or reduce the risk of cancer by avoiding cigarette smoke, UV radiations and bad environment [14].

Theories of Cancer

Almost 6 different theories are present on cancer that how cancer is produced and why it is affected human. Description is given below.

Humoraltheory

Hippocrates reported that four types of fluid are present in our body. When these fluids are un-balanced then disease occurs. Four types of fluids are

a) Blood
b) Black bile
c) Phlegm
d) Yellow bile

He also believed that when black bile is found in excess amount on any site then cancer cause.

Lymph Theory

This theory totally develops on lymph fluid. Any un-balance of lymph fluid causes cancer. this theory is famous until 17th century [15].

Blastema Theory

A researcher name Muller revealed that cancer is made from cell. He also reported that lymph fluid have no contribution in causing cancer [16]. Another scientist name Virchow who was the student of Muller reported that cancer cells were obtained from normal cells [16].

Chronic Irritation Theory

Virchow suggested that cause due to chronic irritation [17].

Trauma Theory

Cancer cause due to trauma and this theory is applicable from 1800s to 1920s.

Parasitic Theory

Researchers concluded that cancer was deadly spread by parasites [11,17].

Etiology

1. In 1911, scientist name Peyton identifies cancer in chicken that is due to Rous sarcoma virus.
2. 1915, cancer produced in rabbit and the reason is coal tar.
3. Cancer is a lethal disease and it is caused by different factor. Like after the discovery of DNA helical structure by Watson and Crick, researcher found that cancer cause due to carcinogens, UV radiations and some cancer are hereditary.
4. In 1970s, two important genes are discovered that name is oncogene and tumor suppressor gene.
5. Proto-oncogene are present in body naturally that controls the cell division. Mutation in these gene result in the activation of oncogene [18,19].
6. Tumor suppressor gene also causes cancer. It is basically a gene that tells the cell to die. Mutations in that gene result in the continuous division and no cell death resulting in the formation of cancer [20].
7. It is also due to the mutation in tumor suppressor gene like mutation in p53 gene causes cancer because p53 is a gene that controls the division of normal cell. Disturbance in this gene result in the formation of cancer. Some other tumor suppressor gene also present that name is BRCA1 and BRCA2. Mutation in these genes causes breast cancer or ovarian cancer [21-23].
8. When a person's gene is mutated or they use chemicals that have carcinogenic properties, then persons have more chances of cancer attack [3,24].
9. In our environment, rate of presence of Hepatitis B, C, HPV, HIV etc. Is high. So, these viruses contribute in cancer. About 7% of cancer are due to viruses, bacteria etc.
10. National Cancer Institute said that people who work in textiles, solvent, plastic and grease industry have high risk of producing cancer [25].
11. Some environmental factors have ability to disturb cellular

mechanism of cell and when cell's mechanism disrupt then it cannot be able to divide cell normally. Also no cell death occurs [22,33].

12. It also occurs due to shortage of methylation in DNA. About 5-6% cancer is due to the shortage of methylation [26].
13. Low number of Monoacetylated H4K16 produce histone modification and these histone modifications related with cancer [27,28].
14. Asbestos is naturally present in environment. Silicon and oxygen are present in asbestos. Asbestos exposure causes cancer.
15. Tobacco is most destructive since 150 years ago. It causes cancer. About 30% of cancer in USA is due to smoking. It is also responsible for lung cancer (87%). It also cause kidney and stomach cancer [29–31].
16. Genetics also plays important role in cancer. If cancer is present in your family then chances present that it may be hereditary. Some tests are present for check that cancer is hereditary or not. When cancer gene detect then this gene can be removed by using different genetic engineering tools.
17. Exposure of benzene causes cancer. It is present is pollution, gasoline etc.
18. Unsafe sex also increase the chance to develop HPV virus and it develop then Breast cancer, vaginal cancer and vulvar cancer are very high.
19. Sun exposure causes many types of cancer like skin cancer, sunburn [32].
20. Human Papilloma Virus causes Penis cancer [30].

Table 2: list of factors that commonly participated in cancer.

Factors	Percentage
Diet	35%
Alcohol consumption	3%
Infection	10%
Pollution	2%
Drug and medical	1%
Tobacco	30%
Environmental factors	3%
Food additives	<1%
Industrial products	<1%
Occupational exposure	4%
Others	3%
Reproductive and sexual behavior	7%

Genes and Molecular Changes that Involves in Cancer

Many genes and molecular changes involve in cancer. As I describe earlier that oncogene and tumor suppressor gene involve in causing cancer. Like XRCC1is a protein that have the ability to repair DNA. It forms a complex by making bond with DNA Ligase III and Polymerase Beta. And this complex is used to repair DNA damage. EGFR is another factor of cancer. It is basically a cell surface receptor and member of ErbB receptor family. Mutation in EGFR leads to cancer [33]. V-Ki-ras2 (KRas) is a protein and it is produce by KRas gene. It plays important role in signal transferring pathway. Mutations in this gene results the formation of cancer. BRCA1 and BRCA1 also contribute in cancer formation. Important reason for cancer is the activation of oncogene.

Many factors involve like point mutation (Ras gene mutated and colon cancer occurs), deletion of Erb-B gene (breast cancer), insertion of C-myc (blood cancer), translocation of oncogene Abl and Bcr (blood cancer) [34]. Chromosome 9 and 22 translocate and led to the formation of chronic blood cancer that diagnose mostly in elder people. In this type of cancer, ph1 (biomarker) produced that is helpful in cancer diagnosis. Found in 90-95% patients [35,36]. p53 are also responsible for cancer. Mutation of this gene in reported in about 60% cancer patients. Cancer remains in cell cycle (G1 and G2 phase) when p53 cooperate with CDC2 and CDK1-P2. p53 activate only for

a) Repair DNA

b) Introduction of cell death

c) Control cell cycle [37–41].

BRM and BRG1 are tumor suppressants and play an important role in lung cancer. Approximately, 15-20% lung cancer is due to these genes. BRG1 destabilize the SWI/SNF complex as a result, cell growth disturb. After destabilization, this SWI/SNF complex reacts with BRCA1, MLL, p53 and RB and causes many types of cancer. Gene's deletion and chromosomal translocations are due to hypomethylation. It affects the promoter and activates the oncogene like S100P in pancreatic cancer, DPP6 and MAGE in melanoma cancer. L1 is a good example of it and it is commonly observed in many types of cancer like breast, bladder and colon.

HDAC is an enzyme that can remove acetyl (de-acetylation). Many classes of HDAC present but sirtuin is most common. SirT1 cooperate with DNMT1 and disrupt DNA methylation. As I write earlier that shortage of DNA methylation also causes cancer. Some microRNAs present that have the ability to regulate its expression. In most cases when oncologists diagnose cancer, they notice that H4K16ac,

H3K4me3, H4K20me3 and H3K27me3 lack [42–44].
Types of Cancer:

Cancer has three common types.

1. Carcinomas
2. Lymphomas
3. Sarcomas

Carcinomas

About 85% diagnosed case are due to carcinomas [11]. It also has further types.

a. Lung Cancer is a type of carcinomas cancer. People use lungs for breathing. Lungs tubes can be spread when air is inhale. Lung cancer also has two types. Small cell lung cancer and second is non-small cell lung cancer. Lung cancer is the main cause of death in USA. Cigarette smoke, alcohol and tobacco are the biggest reason of lung cancer. It diagnose mostly in older people. No symptoms occurs at initial stage but when final stage occurs then symptoms shows like chest and joints pain, weakness, breathing problem etc [33–36].

b. Oral cancer also another type. In this type of cancer, mouth affected. Its causes are tobacco, alcohol, teeth filling etc. Symptoms are difficulty in speaking, yellowish lip, mouth crack etc.

c. Bladder cancer also one of its type. It directly affect bladder. Smoking, chemicals (arsenic, N-nitroso-dibutylamine), work in aluminum sites, plastic industry etc. Its symptoms are blood come through urine, weakness [27,29,31,36].

d. Skin Cancer also cancer type. About 1 million people were diagnosed each year in USA. It is due to X-Rays, sun exposure, chemicals and plastic industries. Skin become red, sun tan, itching etc [28].

Lymphomas

About 7% people diagnose from this cancer. It affects the lymph nodes that are present in human body. In this type, size of lymph node is increase and it became tumor [5–7].

Sarcomas

It affects the mesoderm tissues of body like muscle, bone etc. soft tissue sarcomas is its best example. Radiations, chemicals etc. are the main cause of this disease. About 1% people diagnosed [5].

Table 3: Percentage of cancer in men and women.

In Men	Percentage	In women	Percentage
Prostate	32	Breast cancer	32
Lung cancer	16	Lung cancer	13
Colon cancer	12	Colon cancer	13
Urinary cancer	9	Urinary cancer	8
Leukemia	7	Leukemia	6
Oral cancer	3	Oral cancer	2
Melanoma	3	Pancreas	3
Pancreas	2	Stomach	2
Stomach	2	Urinary tract	4
Other sites	14	Other sites	17

Table4: List of survival rates of different types of cancer.

Cancer	SurvivalRate	CancerType	SurvivalRate
Pancreas	3%	Breastcancer	80%
Liver	6%	Urinarybladder	80%
Esophagus	9%	Leukemia	38%
Lung	13%	Ovary	42%
Stomach	18%	Non-Hodgkin'slymphoma	52%
Nervoussystem	27%	OralCavity	52%
Kidney	56%	Cervix	87%
Colon	59%	Prostate	80%
Hodgkin'slymphoma	79%	Thyroid	95%
Melanoma	85%	Testis	93%

Treatment

Cancer risk is very high in those people whose immune system is suppressed [45].Two scientist name Fehleisen and Busch working independently on disappearing cancer patient. This experiment is held 135 years ago [46]. 1868, Busch was the first person who work on it. He uses erysipelas to infect cancer patient. He noticed that after infecting, cancer cells are shrinking. In 1882, now this time another scientist works on it. He diagnoses the erysipelas and discovered their causative agent. He says that Streptococcus pyogens is the microbe that causes its disease [47,48].

1891, American scientists also works on it. This scientist name is William Coley. He injects the Streptococcus bacteria into those patients who have inoperable cancer. He injects these bacteria because he thinks that these bacteria could remove the cancer cell. And his thinking is successful. He applies this technique on about 1000 different cancer patients and the products which he used are called Coley's Toxin. But this technique faces much criticism from different scientists.

5000 million affected by bone sarcomas every year in USA [49]. 1959, Old et al. performs clinical trials and reported that BCG act as a anti-tumor in mouse model [50]. A title of "Father of Immunotherapy" was given to Coley and Old [51]. Simply immune system has two forms.

1. Innate immunity
2. Acquired/Adapted immunity

Innate immunity is basically naturally present in our body and it includes natural killer cells, dendritic cells, eosinophills, neutrophils, basophils, mast cells and macrophages. It is also called as first line defence.it does not require any change that formed by antigens but adaptive required. It is not present naturally; include helper T-cells, cytotoxic T-cell and B-cells.it requires APC for the activation of immune system that can release specific T-cells and B-cells [52]. Each cell face 20,000 damage DNA per day. These damages are repair by different pathways but sometimes it does not repair and adopt malignant that are identify and destroy by tumor immunosurveillance system. Many Tumor associated antigens (TAA) are present and they include

1. Proto-oncogene
2. Onco fetal agents
3. Over expression of protein etc [53,54]

The idea in which researcher reported that immune system have the ability to identify and destroy foreign malignant cells. This idea is first gave by Burnet and Thomas [55]. Immune system works has three stages.

1. Elimination
2. Equilibrium
3. Escape

In elimination phase, innate immunity identify and destroy the tumor cells while in equilibrium stage, tumor cells who were not killed in elimination phase does not divide and equilibrium state is maintained. And in escape phase, remaining tumor cells are killed.

These tumor cells are protect themselves from T-cells by using immune checkpoints that present on their surface [56]. Monoclonal antibody that name is ipilimumab. It targets the CTLA-4 (cyto-toxic T-lymphocyte-associated antigen-4). Patients live about 20 years more after this treatment. Another drug name nivolumab is also useful in treatment of metastatic melanoma. It target the T-cell proteins where PD-1 is present success rate is 50%. Chlorine is also useful for this purpose [57].

Different treatments are present for treating cancer.

1. Surgery
2. Chemotherapy
3. Radiation therapy
4. Oncolytic Virus
5. Adoptive cell theory
6. Immune checkpoints
7. Cytokines/Vaccines

Surgery

In past, surgery is not very successful for treating cancer because cancer returns back after some time of surgery. The reason is that oncologists do not remove all cells because they do not see clearly inside the body. 1970s, development of ultrasound occur. After this surgeon able to see clearly by ultrasound or Magnetic Resonance Imaging (MRI).In surgery, remove the affected part of body [58,59].

Chemotherapy

In 20th century, surgeons determine a new way for treating cancer patients. Oncologist reported that nitrogen mustard have the ability to kill cancer. They use this way of treatment with surgery. Many drugs are present that use as chemotherapy treatment like Neutropenia, Tamoxifen. But this method of treatment causes many side effects.

Radiation Therapy

X-Rays was discovered in 1896 by Roentgen. After three years of x-rays discovery, radiation use for cancer treatment. Oncologists think that radiations have the ability to cause cancer and it also has ability to cure it. Several types of radiations are used for it like

a. Conformal proton beam therapy

b. Stereotactic surgery and stereotactic therapy

c. Intra-operative radiation therapy.

Oncolytic Virus

It is a newest class of virus that has the ability to treat cancer patients. Researchers modified these viruses in laboratory and totally eliminate its disease causing ability. Then inject in cancer patient on site of infection and lysis the cancer cells. Due to lysis of cancer cells, plethora of tumor antigens released that activate the immune system. T-VEC is first oncolytic virus and approved by FDA in 2015 [60].

Adoptive Cell Theory

It is another type of treating cancer. In this type, isolate T-cells, inoculate it by in-vitro and then placed back into cancer patient. It has many

different mechanisms for acting on cancer e.g. is Chimeric Antigen Receptor T-cell therapy (CART-cell).

Another way of working is by CRISPR/Cas9 (Clustered Regularly Interspaced Short Palindromic repeats with Cas9 associated protein). This system is best for gene editing. It edit gene precisely and accurately. This system was first used in 2012. CRISPR system is naturally present in 40% bacteria and 80% archea immune system. Edit cell by CRISPR/Cas9 was first time used in human in 2016 [59,61,62].

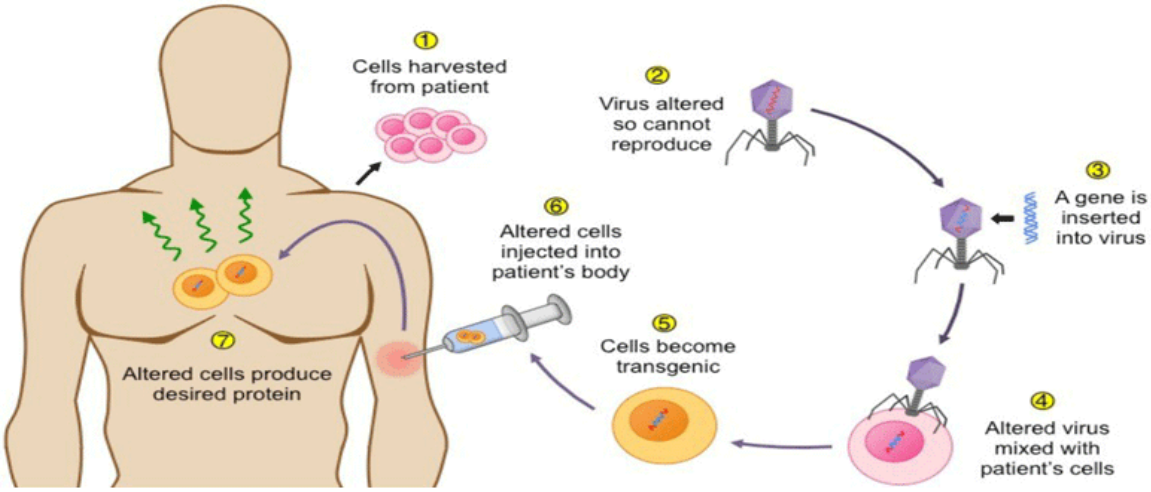

Figure 3. Schematic Diagram for cancer treatment by using oncolytic cells

Immune Check-Points

It is basically a director of immune response. It protects the body, cell or other tissues of body from attacking viruses. It is also used in immune therapy. Approved checkpoints are CTLA4, PD-1 and PD-L1. Some checkpoints are given below.

1. CTLA4 also known as CD152. It is approved in 2011. It targets Bristol-Myers Squibb's Melanoma Dry (Yervoy).
2. PD-1 approved in 2014 and target Keytruda drug (Merck and Co;s Melanoma). It also has the ability to restore immune system
3. B7-H4 also known as VTCN1 and their function is tumor escape
4. KIR also called Killer-cell Immunoglobulin-like Receptor and target Lirilumab.
5. LAG3 also called Lymphocyte Activated Gene-3. It directly target CD8+ T-cells.
6. TIM-3 also called T-cell Immunoglobulin domain and Mucin domain 3. It controls Th1 and Th17 (both are cytokines).
7. B7-H3 also called CD276 inhibitory molecule. Some people working on it and revealed that it target Fc-optimized Monoclonal Antibody[62–68]

Cytokines/Vaccines

Some synthetic cytokines are useful in the treatment of cancer like IL-2 and IFN. L-MTP is bacterial cell wall analogue and is used to activate the innate immunity like macrophages and monocytes. It is used for cancer treatment in many countries but FDA does not approved it[69].

Sipuleucel-T is a vaccine and it is only useful for treatment of cancer by activating dendritic cell. BCG is also useful in bladder carcinomas. BCG release strong types of cytokines like T-helper 1 cells (IL-2, IL-12, IFN-1, TNF) and T-helper 2 cells (IL-4, IL-5, IL-6 and IL-10) [70–72].

Conclusion

As discussed earlier, cancer is the second largest disease that death rate is very high. Its main reason is mutation in tumor-suppressor Gene or activation of oncogene. p53 is the common reason that occur 60% of cancer. Their treatments are very diverse. In past, oncologists adopt surgery method but it is not successful because cancer returns back after surgery. Chemotherapy way of treatment also discovers by researchers and it is used with surgery. After some times, radiation therapy are also discovers but it also has some side effects like head ache, vomiting etc.

Now days, cancer is treated by oncolytic viruses. These viruses are modified in laboratory and remove its disease causing capacity. Then it is injected into cancer patient on site of infection and attack on cancer. Also activate the immune system. Researchers believed that one day this disease will be eliminated from world.

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