

## Cancer disease and its' understanding from the ancient knowledge to the modern concept

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### Abstract

Cancer causes one of the most deaths due to a disease. World Health Organization (WHO) accounting more than 100 countries estimated that the first or second leading cause of death before the age of 70 years is due to suffering from cancer. Worldwide survey counted 19.3 million new cancer cases and almost 10.0 million cancer deaths has been estimated recently. It is a second leading cause of deaths in the United States having more than 1.7 million people diagnosed with cancer and almost 600000 people have died due to the disease. Finding a cure for cancer is one of the greatest challenges over the decades of researches globally until now. Through the ages of time, with the help of enormous research studies, great knowledge on cancer disease has been accumulated. With the advancement of modern technology, understanding on cancer has been partially unwound into a great detail of invisible molecular particles. However, the knowledge of cancer disease and the treatments developed in the ancient times without any of these advanced modern technologies, will keep us amazed always. Are those ancient human beings more intelligent than the modern mankind? Reading these articles cited in this review article makes us wonder.

**Keywords:** Cancer; Ancient knowledge; Hippocrates; Modern concept

### 1. Introduction

The term 'cancer' is a Latin word which was previously known as 'karkinoma' in Greek. The disease had been identified thousands of years ago, before the birth of the Lord Jesus Christ, and the term 'karkinoma' was used by Hippocrates 2300 years ago in describing several kinds of cancer [1,2]. Notably, the Greek physician Hippocrates (ca. 460 – ca. 370 BC) who lived in the age of Pericles (known as Classical Greece) is one of the most outstanding figures in the history of medicine and he is considered as the "Father of Medicine [2,3,4,5,6,7,8]. Hippocrates observed long and distended veins radiating in all sides from a tumor appearing like the limbs of crab or crayfish that extends out of its body and whence the term 'karkinomas' was derived [1,2,9]. His observation was taken from the cut surface of some solid malignant tumours (breast tumors). Hippocrates provided the description by making drawings of skin, nose, and breasts tumours which are outwardly visible, as it was against Greek tradition to open the body and examined. Later, the Roman encyclopaedist, Aulus Cornelius Celsus (ca. 25 BC – ca. 50 AD) translated the Greek term 'karkinos' into 'cancer' which means crab or crayfish in Latin [10, 11, 12, 13, 14]. Further, the Greek physician Claudius Galenus (also known as Galen; ca.130- ca. 200 AD) implemented the Hippocrates theory and proposed black bile and yellow bile caused incurable and curable cancer respectively; he began to use another term 'oncos' (means swelling in Greek) to describe any benign tumours, reserving Hippocrates' using of the term 'karkinos' for malignant tumours [14,15,16]. Galen also added -oma

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as suffix giving the name carcinoma (or karkinoma) to indicate cancerous lesions [16] and from his uses the modern word oncology was derived. However, the description of human cancer had been noted much earlier by Egyptians. It was first described in the Edwin Smith Papyrus dated 3000 BC that illustrated a case of breast cancer. Moreover, several other types of tumors such as of skin, uterus, stomach, and rectum were recorded in other available documents including Ebers Papyrus dating from 1500 BC. In these old Egyptian documents cancer was described as grave incurable disease and believed to be the curse of the gods [12, 14].

From the time of Hippocrates to the post genomic era today, thousands of theories and scientific findings have paved the way to a far better scientific understanding of cancer today and modern approaches to this disease are based on many of these theories as fundamental. Since there are many diseases that are developed due to uncontrolled division of cells in the body, cancer comprises a large group of diseases which are more than 100-200 diseases [1, 10, 17, 18, 19, 20, 21, 22]. While cancer may develop in any part of the body tissues or organs with each type having unique features, the basic processes of developing into cancer are quite similar in all forms of the diseases [17, 23, 24]. When the abnormal body cells start to grow uncontrollably, they move beyond their usual boundaries of the tissue or organ and invade/spread into the adjoining areas and/or to other parts of the body organs. The latter process of spreading or invading to organs is called metastasis which is a major cause of death from cancer.

## **1.1. Increasing burden to human life by cancer**

### *1.1.1. Global statistics*

With the advance technology in diagnosing cancer and more awareness, the number of cancer occurrence and causing deaths by the disease continue to increase over the years. The increase of life expectancy, epidemiological and demographic transitions also play role upon this rise [25, 26]. In the latest survey of WHO, 18.1 million people across the world were affected by cancer in 2018 and 9.6 million people were died from the disease in the same year [26]. According to the report, following the current trend of the increase, it is suggested that, the number individuals affected and the dead by the disease will be nearly double in the next 20 years of time. And the highest increase is expected to happen in the low- and middle-income countries (LMIC), where more than two thirds of the world's cancers will occur that based on the present scenario [26]. In 2016, 71% of all deaths were reported to be caused by non-communicable diseases (NCD), thereby leading cause of death globally [26, 27, 28, 28, 30]. Of the 15.2 million premature deaths which were among the adults aged from 30 to 69 years, 4.5 million (29.7%) were due to cancer [27, 28]. Cancer is the first or second leading disease that causes premature death in 134 of 183 countries in the world as it is responsible for causing death of one in six deaths globally [26,31].

Among the 600 or more types of cancer listed by the International Classification of Diseases revision 11<sup>th</sup> (ICD-11), the lung cancer is the most common cancer with 11.6% of all cases while female breast cancer and colorectal cancer stands at 2<sup>nd</sup> and 3<sup>rd</sup> most common cancers with 11.6% and 10.2% respectively [26]. Most death due to suffering from cancer is caused by lung cancer with 18.4% of all deaths, followed by colorectal and stomach cancer with 9.2% and 8.2% of all deaths respectively [26]. In Global cancer statistics 2020 report which was carried out with 36 cancers in 185 countries showed female breast cancer to be the most common cancer with 11.7% followed by lung cancer and prostate cancer with 11.4% and 7.3% respectively [32]. However highest number of deaths due to cancer is the lung cancer with 18.0% deaths which is similar with the WHO report 2020; then followed by Liver cancer 8.3% and female breast 6.9% [32]. On the other hand, the most common cancer type varies among countries. For example, certain cancers such as cervical cancer and Kaposi sarcoma are found to be more common in countries at the lower end of the human development index (HDI) when compared with the high-HDI countries [26]. And the lower access to effective treatment is the reason for higher fatality rates in lower HDI countries as well as the diagnosis at later stages and lack of treatment.

### *1.1.2. Indian context*

India's latest cancer statistics report 2020 from National Cancer Registry Programme also agreed with the global estimate on non-communicable diseases causing highest number of deaths. Non-communicable diseases are accounted for 63% of all deaths in India in which cancer is one of the leading causes of deaths with 9% of the deaths [33, 34]. Lung cancer and oral/mouth cancer were the most common cancers among males in the Indian subcontinent [29]. Lung (9 PBCRs), mouth (9 PBCRs), esophagus (5 PBCRs), stomach (4 PBCRs), and nasopharynx (1 PBCR) cancers were the most common cancers in men whereas breast cancer (19 PBCRs) and cervix uteri (7 PBCRs) were the most common cancers in women. Notably the highest rate cancer incidence occurred in the North Eastern (NE) and more number of males suffered from the disease compared to females at the rate of 6:4. Moreover, among the NE states, grater rate is observed in Aizawl district showing 7 (male) and 4 (female) times of that of Osmanabad and Beed district population-based cancer registries. The reason is because of the lack of required infrastructure for specialized treatments and human resources as compared to the rest of India.

In case of Manipur, the cancer rate is relatively low when compared with other North East states and the other parts of India. According to the data collected by various population-based cancer registries and hospital-based cancer registries across India under the National Cancer Registry Programme–National Centre for Disease Informatics and Research of Indian Council of Medical Research, there is 1 in 14 individuals found to be risk of cancer and 20.5 deaths caused by the disease per 100000 persons, in males; whereas in female, 1 in 12 individuals is found to be risk with the disease and 17.3 deaths per 100000 individuals [33]. Subsequently, when district wise incidence was considered, Imphal west has the highest number of cancer patients with 1 being risk per 9 individuals and 29.6 deaths per 100000 individuals, among males; and in females, 1 risk per 8 individuals and 24.3 deaths in 100000 individuals had been recorded. These data were collected during 2012 to 2016 using International Statistical Classification of Diseases and Related Health Problems, 10th revision: C00-C97.

### **1.2. Understanding of cancer through the ages until 18 century**

It is believed that human cancer had been existing from before the prehistoric time as indicated by paleopathologic findings and investigation on ancient mummies of Egypt [35, 36]. Ancient Egyptian records written on papyrus revealed that cancer disease had occurred as old as 3000 years before the birth of Lord Jesus Christ [11, 12]. The first written description of cancer based on the knowledge of surgery and medicine was found in the Edwin Smith Papyrus dated 3000 BC and the Ebers Papyrus dated 1500 BC [37,38]. The written description on 15 feet long Edwin Smith Papyrus contained 48 case reports including description on breast cancer/ulcer from 8 cases (believed to be the oldest report on cancer) and concluded with no treatment availability [36,37]. In the Ebers Papyrus which has 110-page scroll and about 20 meters long [39], enlarged thyroids and polyps along with the tumors of the skin, pharynx, stomach, rectum and uterus are described. [36, 38, 40].

The Greek physician Hippocrates' theory on cancer has been widely cited in several articles as the first scientific conceptualization on cancer. This means the scientific knowledge on cancer has been developed ever before 400 years before Christ. Interestingly, Hippocrates was also a pupil of Aristotle and called him as 'the Great Physician' [8]. He separated the superstitious and religious belief of disease and medicine and initiated scientific concepts and cultured them [27]. He classified diseases including cancer based on the primary symptoms and drew conclusions [11, 41, 42]. Hippocrates described cancer as growing tumors that occurred mostly in adults looking like a moving crab and thus the terms carcinos (a tumor), carcinoma (a malignant tumor) and cancer (a nonhealing malignant ulcer) were derived. And the hard tumor, the scirrhus, was found to be different from carcinos and carcinoma [40, 43]. Notably, Dr. Steven Hajdu a cancer pathologist has thoroughly narrated the history of cancer in detail in his well cited 7 published articles [12, 44, 45, 46, 47, 48, 49]. Hippocrates proposed that tumors were caused by an imbalance of blood, phlegm, yellow bile and black bile etc. and among which the black bile was particularly bad. The dark and beef glaze-like vaginal discharge was to be associated with enlargement and ulceration of the uterus. He also wrote about cancers of the skin, mouth, breast, and stomach as well as deep-seated tumors in the armpit, groin, and thigh in older people etc. Further, breast carcinoma with bloody discharge from the nipple, scirrhus tumor of the cervix association with bleeding, emaciation, and dropsy, which led death were also described. He mentioned superficial and deep-seated tumors in the armpit, groin, and thigh in older people.

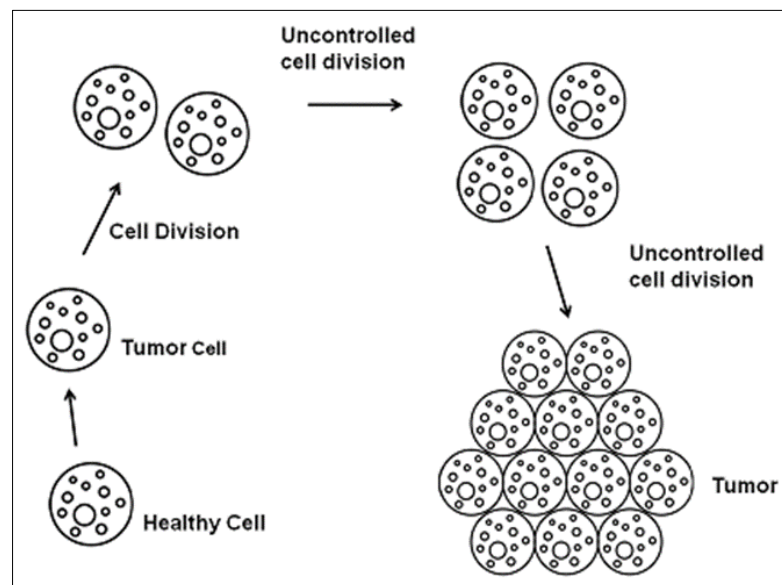
Through time with advances in education, Hippocratic theory had been taken into greater level of scientific understanding on cancer. Aulus Cornealius Celsus (25 BC– 50 AD), an encyclopaedist and a native of Greece, had continued on Hippocratic approach by comparing cancer with a crab and he observed cancer adhered to surrounding tissues like a crab grappling on to anything in its claws [50]. He categorized several types of the disease including face, mouth, throat, penis, liver, spleen and colon cancers [51]. Celsus also introduced the first classification of breast carcinoma in his text book *De Medicina*, a 1st-century medical treatise. Furthermore, He differentiated early carcinoma, carcinoma without ulceration and ulcerated fungating carcinoma [50, 51]. Claudius Galen (131 AD 200) another Greek physician who followed Hippocrates also adopted the black bile theory. He also believed that black bile caused severe, ulcerated and incurable cancer; whereas thin bile caused nonulcerated and curable cancer [51, 52]. He also observed the similar appearance of cancer growth with the crab and advised surgical removal of the tumor by cutting the surrounding healthy tissue. He strongly believed that cancer was to be a constitutional disease that particularly affects those with a melancholic disposition [51, 52]. Interestingly, while the first Roman physician of excellence 'Aulus Cornealius Celsus' was forgotten, 'Claudius Galen's rigid humoral theory was promoted. Because Galen's authoritative reasoning left no questions unanswered. And thus, it happened that Galen's canonical theories obstructed the progress in medicine and delayed in further understanding about cancer until the end of the 18th century [11].

### **1.3. Modern concept of cancer and/or the hallmarks of cancer**

With the fast development of advanced technologies, various researches in the last 60 years have brought much deeper knowledge and understanding on cancer. The advance knowledge on human genome and the discovery of mutations

that produce oncogenes with gaining dominant functions as well as the loss functions of recessive tumor suppressor genes, revealed involvement of dynamic changes in the genome, in causing cancer. This gain or loss of function has been identified in human and animal cancer cells experimental model systems [53]. In this regard Theodor Boveri (1862-1915) and Marcella O'Grady Boveri (1865-1950) had been well acknowledged for their clear concept and significant contribution which described in the article 'the chromosome theory of cancer' [54,55]. Now the principle has been further expanded with deeper gain of knowledge and thoughts, emphasizing the cause of cancer that involved incredible heterogeneity with behaviors, genes and pathways. Hanahan and Weinberg summarized these principles in their article "The Hallmarks of Cancer" that has gained wide recognition for introducing to this present concept on Cancer [56].

There are several lines of evidences which indicate involvement of multistep processes that reflects genetic alterations driving to the progressive transformation of normal human cells into highly malignant derivatives, that occur in tumorigenesis in humans. Many types of cancers in human occurred with an age-dependent incidence which implicates four to seven rate-limiting, stochastic events [57, 58]. Pathological examination of various organ sites showed lesions that appeared to represent intermediate steps which have occurred via progressive evolving of cells into becoming invasive cancers from normal state, passing through series of premalignant conditions [59]. This indicates that the genomes of tumor cells are invariably altered at multiple sites, due to having suffered disruption through lesions indirectly by point mutations and directly through changes in chromosome complement [56, 60, 61, 62]. Moreover, transformation of cultured cells requires multistep process. At least two genetic changes are required to transform rodent cells before they acquire tumorigenic competence; which is difficult to do so in human cells with the similar experimental conditions; this further revealed a more complicated biology in human [63,64,65,66]. The involvement of multiple rate-limiting steps in tumorigenesis had been consistently supported in various studies that have used transgenic mice models of tumorigenesis [56, 67, 68, 69, 70, 71].



**Figure 1** Diagrammatic representation of uncontrol cell division in tumour development from normal cell

Subsequently, when we consider the existence of several types of cancer occurring within the same tissue, finding ways of clear understanding the underlying mechanism of each type is even more complicated. Without any doubt, one can assume several distinct regulatory pathways operating within a target cell in order the cell to becoming cancerous. Several questions arise on whether the same set of the regulatory pathways would be disrupted in the cells of disparate neoplasms; which pathways operate in a cell-autonomous basis and coupled to the signals received by the cells from their surrounding microenvironment within the target tissue; how could the large and diverse cancer associated genes be channelized into operating a small group of regulatory pathways.

Due to this highly complex biology of cancer, it has been difficult for the researchers to channelize these events underlying human cancer. At this juncture, Hanahan and Weinberg (2000) thoughtfully organized the vast records of cancer cell genotypes into the manifestation of six essential alterations in cell physiology that collectively dictate malignant growth of cancer, termed as six hallmarks of cancer [56]. The proposed six hallmarks of the disease are

- Self-sufficiency in growth signals
- Insensitivity to growth-inhibitory (antigrowth) signals
- Evasion of programmed cell death (apoptosis)
- Limitless replicative potential
- Sustained angiogenesis and
- Tissue invasion and metastasis

They suggested that these six features are shared in most human tumors. Because each of these physiologic changes acquired during tumor development, signifies the failure of an anticancer defense mechanism hardwired into cells and tissues [56]. The authors further updated their concept adding two more emerging hallmarks after 10 years [72].

- Reprogramming of energy metabolism and
- Evading immune destruction

This thoughtful concept of Hanahan and Weinberg has been highly appreciated and cited in thousands of articles. The detail modern concept will be discussed in our next article.

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## 2. Conclusion

The scientific understanding on cancer had been well advanced even before thousands of years, during the ancient times. People born in the modern era exposed in the highly advance technologies will always wonder, how the ancient people could derive such intelligent thoughts without using any of these modern tools. Thanks to the advanced treatment and diagnostic approaches, survival rate of cancer has been increased over time.

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## Compliance with ethical standards

### *Disclosure of conflict of interest*

Authors declare no conflict of interest.

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