Tumor Biology: An Introduction

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The gene that enables birds to learn songs can become cancer-causing. There is no normal physiological process that can't be bastardized by the disease.

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Abstract

About 200 different types of cells and their coordination make up and run the human body. And each of these cells is governed by the genetic information encoded in the DNA present in the cells' nuclei. Although the nucleotide sequence of DNA is well checked and maintained throughout one's life, mutations still occur that in certain instances cause diseases, cancer being one of them. The failure of the intricate genetic system that balances cell birth and cell death causes cancer. Cancer cells are clonal as a single common ancestral cell gradually accumulates mutation to form a tumor that over time develops malignancy. Growth factors are important components of tumor microenvironment that provide heterogeneity and autonomy to cancer cells, the properties that normal cells lack. Not only spontaneous mutations and genetic predisposition but also lifestyle, to a great extent, contributes to carcinogenesis. Tobacco smoke, UV

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rays, X-rays, agents that attack DNA, and change in its chemical structure are potential carcinogens. Viruses too can cause carcinogenesis. Whatever be the causes, they all affect the fundamental aspects of cellular function, including DNA repair, cell cycle regulation, apoptosis, and signal transduction. Thus, correct and effective management of this fatal disease is only possible if the underlying biological complicacies are well understood.

Keywords

Carcinogen · Mutation · Neoplasm · Oncogene

3.1 Introduction: Cancer Perspective from Fundamental Biology

In the sum of the parts, there are only the parts. . . ., as Wallace Stevens stated, this can be well explained in the context of living organisms. Comprehending the diversity among organisms in practical terms is to understand the differences in structure, function, and behavior of cells that are the basic or fundamental units of a living organism. Every organism either consists of a single or multiple cells. The human body is composed of about 200 different types of cells, each with a specific function that works as a whole in a coordinated manner, to define the overall function of the organism. However, all cells share common fundamental properties that have been conserved throughout evolution. The discoveries of biochemists and molecular biologists suggest that all cells contain genetic information, generally in the form of deoxyribonucleic acid (DNA) and utilize the same basic principles of energy metabolism.

We now know that genes, which chemically are composed of DNA, ultimately define the biological structure and maintain the integration of cellular function. A cell, during reproduction, replicates its DNA and then passes a copy of the genetic information encoded in the form of DNA to its progeny, by dividing it into two daughter cells. The gradual understanding of this transmission of genetic information as a result of closer insight into the properties of genes, their composition, variation among them, and the role they play in heredity led to the emergence of altogether a separate branch of biology called *genetics*. However, the seed to the emergence of this discipline was sown much before genes contained in DNA were found to be the actual genetic material.

The true understanding of genetics in scientific terms began in a monastery garden in Central Europe, back in the 1860s, where an Augustinian monk named Gregor Johann Mendel, through a set of simple experiments on pea plants, determined the underlying principles of heredity and made some generalizations that later came to be known as *Mendel's laws of inheritance* namely the law of dominance and uniformity, law of segregation, and the law of independent assortment. The essence of all of them is based on the fact that each trait in an organism is controlled by *a pair of factors* (later termed *genes*), one *dominant* and the other *recessive*, and that during

gamete formation members of a gene pair separate from each other. Although his works were published in 1866, its true significance was understood about three decades later when Hugo de Vries and other scientists rediscovered his research (Klug et al. 2016).

Owing to the discovery of chromosomes by Flemming in 1879, almost contemporaneously with the rediscovery of Mendel's work, two cytologists Sutton and Boveri observed that chromosomes and Mendelian factors have several properties in common and behaved as per Mendel's principles during gamete formation (*meiosis*). This parallelism called the *chromosome theory of inheritance* laid down the foundation for the physical basis of inheritance and it was further confirmed through subsequent works of Morgan and others that genes contained in chromosomes were the actual message bearers, transmitted through gametes, carrying hereditary information faithfully from generation to generation.

However, in the subsequent years, modification and extension of Mendelian principles and the study of interallelic interaction followed by elucidation of the structure of DNA in 1953 by Watson and Crick took us a bit closer to—*what could be a gene* in chemical terms. Further advancements in molecular biology and deciphering of the genetic code contained in the ATGC nucleotides' sequence in DNA led to better understanding of how the combined effect of genes and their products interacting with the environment control the *phenotype* of an organism as a whole and the biology of diseases in particular. As per the central dogma in molecular biology, the genetic code in a DNA sequence is utilized to synthesize mRNA (transcription), which in turn specifies the amino acid sequence in polypeptides and thus proteins (translation), whose specific molecular organization and function determine the phenotype of the organism. However, genetic code is not the absolute determiner of gene expression. Although all the cells in an organism contain the same DNA, they differ in the activation of selective genes at a specific time and in specific tissues in response to specific environmental stimuli. This differential gene expression could be manipulated at genomic, transcriptional, post-transcriptional, translational, posttranslational, and hormonal levels mediated through a variety of ways like DNA rearrangements, the effect of transcription factors, mRNA processing and export from the nucleus, gene silencing by noncoding RNAs, chromatin remodeling, and the effect of growth factors (Cooper 2000; Klug et al. 2016).

Although these processes are finely tuned and nevertheless DNA is a highly stable molecule, copied with high accuracy, changes in DNA structure do occur, which may alter the genetic information of the DNA, leading to mutations. On one hand, when mutation provides the raw material for evolution, when it harms the phenotype of an organism, it causes a genetic disorder or a disease.

Given the vast number of activities that need to be coordinated in every cell, it is not surprising that malfunctions occasionally arise. Cancer, the second leading cause of death after cardiovascular disease (Dagenais et al. 2020), is a prominent example of a disease that arises from such abnormalities in cell function. Cancer is not a single disease rather a hundred different diseases. All cells grow, may differentiate, and die after a predetermined time. When the intricate genetic control system that balances

cell birth and death fails, cell immortality occurs that leads to cancer. According to the clonal evolution theory of cancer, most cancers come about from a progressive series of genetic changes. The mutations can be point mutations that directly affect the DNA sequence or as in most cases, as recent research has revealed, they could be chromosomal aberrations affecting the types and locations of chromatin modification, particularly DNA and histone acetylation patterns. Some of these mutations are results of epigenetic modifications as well that can be inherited from one cell to its progeny cells and may be present in either somatic or germ-line cells. However, these mutations occur predominantly in somatic cells. Thus, cancer although being a genetic disease is not always heritable. Only about 1% of cancers are associated with the germ-line mutations that increase a person's susceptibility to certain types of cancer. Whatever be the source or type of mutations, they affect the fundamental aspects of cellular function, including DNA repair, cell cycle regulation, apoptosis, and signal transduction.

3.2 The Nature of Cancer and Its Types

A multicellular organism starts its life from a *zygote*, which through a regulated and controlled manner of cell divisions develops into an embryo, finally becoming a fully grown organism. The mechanisms of cell growth and division are well checked and controlled throughout one's life unless rendered ineffective by some *tumorigenic effect*. When such a mutative condition leads to abnormal and uncontrolled cell divisions, the cells become congregated locally in a particular place to form a swelling called tumor. If the tumor remains less harmful, being restricted to the tissue of their origin, they are called benign. On the other hand, malignant tumors are those from which cells detach and migrate through blood or lymph systems to the other parts of the body, giving rise to secondary tumors. The second type is the cancerous one. Thus, apart from uncontrolled cell growth and division, the second most important fundamental property of cancer cells is *metastasis* during which the tumor cells undergo abnormal cytoskeletal changes, dissociate from the primary tumor secreting proteases that breach the components of *extracellular matrix* and *basal lamina,* and invade other tissues (loss of contact inhibition) (Wagener et al. 2017; Weinberg 2014).

Tumors are a mixture of cells, some of which act as *cancer stem cells*, each of which has the capability of both self-renewal and differentiation into a mature cell type. The tumor microenvironment contributes to the *heterogeneity* of cells within the tumor. However, all cancer cells are clonal; that is, they originate from a common ancestral cell that accumulates specific mutations. This means that a single mutation is not sufficient to transform a normal cell into a tumorigenic, malignant one. Cancer is initiated when a single mutated cell begins to proliferate abnormally, progressively gathering additional mutations, and the selection and proliferation of specific rapidly growing cells from the whole population ultimately cause malignancy.

Apart from spontaneous mutations and to some extent genetic predisposition to certain types of cancers, lifestyle has been found to directly or indirectly influence

carcinogenesis, occupation, and diet being the two other main factors. Epidemiologists suggest that there is a 20-fold increased risk (Dela Cruz et al. 2011) of developing lung cancer in patients smoking tobacco that contains at least 60 chemicals that can alter DNA sequences. Similarly, alcohol consumption increases the risk of liver cancer (Marengo et al. 2016). Inhaling asbestos fibers may cause *mesothelioma*. Consumption of red meat and animal fat is associated with prostate, colon, and breast cancers (Kvale et al. 2017; Bray and Kiemeney 2017; World Cancer Research Fund/American Institute for Cancer Research WCRF/AICR 2018). The most potential chemical mutagens can be both naturally occurring (e.g., aflatoxin, component of a mold) (Lin et al. 2014) and synthetic compounds (e.g., nitrosamines and pesticides). These chemicals can directly act as mutagens or are converted to mutagenic compounds by cellular enzymes.

Most cancers fall into three major categories based on the embryonic tissue of their origin: carcinomas—malignancies of epithelial cell lining of various organs, like mouth, esophagus, intestines, and uterus, and also from the skin; sarcomas—solid tumors of connective tissues, arise from *mesodermal* cells of connective tissues like fibrous tissue and bone; and leukemias or lymphomas arising from blood-forming cells and cells of the immune system, respectively. However, some types of tumors do not fit into these major classifications. About 200 varieties have been described, whose properties and treatments are different. Leukemias of early childhood differ from adult leukemias in their properties and treatments.

Cancers are named according to the organ from which they arose. Retinoblastoma is mainly cancer of the eye, osteosarcoma of bone, and melanoma of skin pigment cells. The most common solid organ malignancies arise in the lung, breast, and gastrointestinal tract. Females have the highest lifetime risk of breast, lung, and bowel cancers; prostate, lung, and bowel cancers are prevalent in men. Cancers of lung, liver, stomach, and bowel are the most common causes of cancer death worldwide, accounting for more than four in ten of all cancer deaths. The rate of death varies greatly for different types of cancer. Lung cancer and pancreatic cancer are the worst, usually fatal within a year. But not all cancers are fatal, only one-fifth of breast cancer cases results in death (Bray et al. 2018).

3.3 Environmental Insults—Mutagens, Carcinogens, and Cancer-Causing Mutations

Sir Percivall Pott, a British surgeon, in 1775 became the first person to link malignancy with environmental carcinogen when he found an association between high incidences of an uncommon form of scrotal cancer called "chimney sweeps' carcinoma" and exposure to soot. This provided the first evidence of direct contact carcinogen to skin, i.e., soot, and indicated an occupational link to cancer (Pott 1775; 1974). Thereafter, isolated carcinogenic chemicals from soot along with several other compounds have been found to cause cancer in laboratory animals. Apart from these chemicals, many other types of agents including ionizing radiations and RNA- and DNA-containing viruses have been identified as potential carcinogens.

Ultraviolet radiation, the leading cause of skin cancer, may act as a direct mutagen. However, some carcinogenic chemicals, such as those present in soot or cigarette smoke, can act as direct mutagens or may be converted to potential mutagens by cellular enzymes. *The commonality in all these agents lies in the fact that all of them alter the genome.*

There are different ways by which a normal cell could acquire cancer-causing mutations. Environmental abuses like tobacco smoke, UV rays, X-rays, agents that attack DNA, and change in its chemical structure could result in such mutations. Mutations could arise from spontaneous errors during cell division. There is some chance of error during the DNA copying process (replication), such as an adenine (A) base is replaced by guanine (G) or cytosine (C). Some hereditary cancer syndromes, such as retinoblastoma and breast cancer, could be inherited from parents through mutant cancer genes. Still, inherited cancers probably account for 5–10% of all cases. In some cases, genes could also be carried into the cells through viruses. In all these cases, the result converged on the same pathological process—the inappropriate activation or inactivation of genetic pathways that controlled growth, causing the malignant, dysregulated cellular division that was characteristic of cancer.

Five leading behavioral and dietary risks, high body mass index, low fruit and vegetable intake, lack of physical activity, tobacco, and alcohol use, have been found to cause about one-third of deaths from cancer (Dela Cruz et al. 2011; Marengo et al. 2016; Kvale et al. 2017; Bray and Kiemeney 2017; World Cancer Research Fund/American Institute for Cancer Research WCRF/AICR 2018; Pott 1775; International Agency for Research on Cancer IARC 2014). Tobacco remains the leading factor in the etiology of 33% of cancers, including those of the HNSCC (head and neck squamous cell carcinoma), lung, nasopharynx, bladder, and kidney, and these could be prevented through reduction in smoking of the populace. Further 30% of cancers, including those of the breast, colon, esophagus, stomach, and liver, have been associated with diet, alcohol, obesity (high BMI), and lack of physical activity (sedentary lifestyle). Several modifications in lifestyle like reduced consumption of red meat, animal fat, and alcohol and increased intake of fiber, fresh fruit, and vegetable would prevent obesity and thus cancer. Vaccination and control of infections in cervix, stomach, liver, nasopharynx, and bladder may reduce the risk of about 15% of cancers.

3.4 Infectious Agents, Inflammation, and Cancer

The relationship between viruses and human cancer remained hypothetical until 1980 when Robert Gallo at the National Institutes of Health first found a *retrovirus* (human T-lymphotropic virus type 1) is responsible for a rare form of leukemia (Poiesz et al. 1980; Gallo et al. 1982). Work by Gallo's team and independent work in Japan by K Takatsuki showed that adult T-cell leukemia (ATL) was caused by HTLV-1 and the disease is highly prevalent in Japan and sporadic in most of the remaining parts of the world (Gallo et al. 1982; Yoshida et al. 1982). Some DNA

viruses like *polyomavirus*, *simian virus* 40 (SV40), *adenovirus*, and *herpes-like viruses* can cause human cancers. However, about 15% of cancers worldwide are linked to other types of viruses. Mostly, these viruses, rather than acting as the sole cause of cancer, greatly increase the risk of its development. The human *papillomavirus* (HPV) provides a good illustration of relationship between viral infection and cancer. Transmission of this virus can occur through sexual activity, and its frequency is increasing in the population. Although the virus has been found to be linked with the development of about 90% of cervical cancers (Walboomers et al. 1999), the vast majority of women who have been infected with the virus will never develop this malignancy. HPV also induces the development of mouth and tongue cancers in both males and females. An effective vaccine against HPV is now available (Herrero and Murillo 2018). Other viruses like *hepatitis B virus* is associated with liver cancer (London et al. 2018), *Epstein–Barr virus*, associated with Burkitt's lymphoma (Brady et al. 2007), and a type of *herpes virus* (HHV-8), associated with *Kaposi's sarcoma (*Ablashi et al. 2002).

Helicobacter pylori, a bacterium living in the stomach, which is also responsible for ulcers, is associated with certain gastric carcinomas (Plummer et al. 2015). Recent evidence suggests that chronic inflammation triggered by the presence of the pathogen is linked to many of these cancers. For example, inflammatory bowel disease (IBD), a result of chronic inflammation, increases the risk of colon cancer (Rubin et al. 2012). Further findings of the general process of inflammation help elaborate its role in cancer development, which was much unexplored previously.

3.5 Cellular and Genetic Basis of Cancer

3.5.1 Comparison of Cancer Cell and Normal Cell

Cancer cell acquires a few noticeable properties, which are different from a normal somatic cell that favors them to become a neoplasm growth (Cooper 2000; Wagener et al. 2017; Weinberg 2014). Whether in vivo or in vitro, cancer cell loses their growth control and become malignant. These malignant cells can grow continuously on their own irrespective of the presence or absence of growth stimulatory or inhibitory signals that otherwise influence the growth of normal cells. When normal cells are grown in culture, they are usually supplemented by serum that contains essential growth factors, such as epidermal growth factor. But as cancer cells are independent of the regulatory mechanisms that govern normal cell proliferation and survival, they do not require growth factors for their proliferation. Normal cells, after dividing mitotically for a certain time, cease to continue their growth and division by undergoing senescence. On the contrary, the presence of telomerase in cancer cells (being one of the reasons for higher growth potential than normal cells) allows them to divide indefinitely, rendering them immortal. The absence of telomerase from most types of normal cells is thought to protect the body against tumor growth. Apoptosis is another important savior mechanism characterized by self-destruction of normal cells when the chromosome content in them is disturbed. In contrast,

cancer cells fail to elicit apoptotic response even when their chromosome content becomes highly deranged.

3.5.2 Genetic View of Cancer

Single-gene mutations do not cause most common human diseases. Rather multiple genes spread diffusely throughout the human genome and determine the risk for a genomic illness. These diseases can be understood, diagnosed, or predicted only by understanding the underlying interrelationships between several independent genes.

3.5.3 Tumorigenesis

Cancer is an ultimate result of a multistep process that accumulates some sequential tumorigenic gene mutations. To initiate carcinogenesis successfully, cells require certain characteristics, collectively referred to as the "hallmarks" of cancer (Hanahan and Weinberg 2000). Cancer is an archetypal genomic disease, and its genetic nature had been known since 1872 when Hilario de Gouvea, a Brazilian ophthalmologist, had described a family in which a rare form of eye cancer, called retinoblastoma, coursed tragically through multiple generations (Monteiro and Waizbort 2007). Despite bad habits, bad recipes, neurons, obsessions, environments, behaviors, and other attributes shared by families, the familial pattern of the illness suggested the role of an *inherited factor* as proposed by deGouvea as the cause of retinoblastoma. Some light on the *inherited factors* in peas was already cast by an unknown botanist monk named Mendel seven years prior in a publication. However, de Gouvea had never encountered Mendel's paper or the word gene.

By the late 1970s, a full century after de Gouvea, scientists began to converge on the uncomfortable realization that cancers arose from normal cells that had acquired mutations in growth-controlling genes. These genes act as powerful growth regulators in normal cells. Hence, a wound in the skin, having healed itself, typically stops healing and does not morph into a tumor. Here, genes tell the cells in a wound when to start growing and when to stop. In cancer cells, these pathways were somehow disrupted. Start genes were shut off, and stop genes were ceased; genes that altered metabolism and identity of a cell were corrupted, resulting in a cell that did not know to stop growing.

Alterations of such endogenous genetic pathways caused cancer—a *distorted version of our normal selves*, as Harold Varmus, the cancer biologist (Varmus et al. 2016), but it was ferociously disquieting as for decades, scientists had hoped that some pathogen, such as a virus or bacterium, would be implicated as the universal cause of cancer and might potentially be eliminated via a vaccine or antimicrobial therapy. The gradual unveiling of correlation between cancer genes and normal genes threw open a central challenge of cancer biology. How the mutant genes are restored to their off or on states while they allow normal growth to proceed unperturbed remains the biggest conundrum of cancer therapy.

3.5.4 Oncogenes and Tumor Suppressor Genes

Basically, the two classes of genes—tumor suppressor genes and oncogenes—have been implicated in carcinogenesis (Cooper 2000; Klug et al. 2016). Tumor suppressor genes encode proteins that restrain cell growth and prevent cells from becoming malignant, thereby acting as cells' brakes. Oncogenes, on the other hand, encode proteins that may cause genetic instability, prevent apoptosis, promote metastasis and as a whole shatter the growth control, and promote the conversion of a cell to a malignant state. Most oncogenes act as accelerators of cell proliferation. *The existence of oncogenes and tumor suppressor genes suggests an elaborate system to positive and negative controls that maintain cell growth within normal limits.* Taken separately, the oncogenes and tumor suppressor genes provide alternate pathways of oncogenesis. *Mutation of oncogenes stimulates mitogenic pathways, resulting in cell proliferation. Loss of control of cell proliferation* can be brought about by mutations in tumor suppressor genes.

3.5.5 Genome-Wide Approach

It was remaining as a big question to the cancer biologist that how much such genes were involved in causing a typical human cancer, one gene per cancer, or, dozen and even hundred. In the late 1990s, at Johns Hopkins University, a cancer geneticist named Bert Vogelstein decided to create a comprehensive catalog of nearly all the genes implicated in human cancers (Vogelstein et al. 2013). *Vogelstein had already discovered that cancer arises from a step-by-step process involving the accumulation of dozens of mutations in a* cell. By acquiring sequential mutations, gene by gene, a cell leads to the dismantling of its growth regulatory pathways and proceeds toward cancer.

To cancer geneticists, these data suggested that the one-gene-at-a-time approach would be insufficient to understand, diagnose, or treat cancer. A fundamental feature of cancer is its enormous genetic diversity. Two specimens of breast cancer were removed from two breasts of the same woman at the same time and might have vastly different spectra of mutations and thereby behave differently, progress at different rates, and respond to different chemotherapies. To understand cancer, biologists would need to assess the entire genome of a cancer cell.

3.6 Temporal Variation of Cancer Incidence Rate in Different Populations

Several studies on migration have established that the frequencies of various cancers vary greatly between countries and also in ethnicity (Bray et al. 2018; International Agency for Research on Cancer IARC 2014; Herrero and Murillo 2018; London et al. 2018). Thus, not just genetic but environmental differences do affect the prevalence of various types of cancer; second-generation Japanese in California

have a tenfold higher death rate from prostate cancer than do Japanese in Japan. Various epidemiological studies enlighten the effects for various carcinogenic agents. For example, meat and some high-calorie, fat-rich diet can be cancer-causing. Women from countries that consume high quantities of meat (12 pounds per day) possess tenfold higher risk of developing cancer. Japanese have a high level of stomach cancer correlated with consumption of fern fronds. Incidence rates of stomach cancer among first-generation Japanese migrants to Hawaii were interestingly decreased than the rates among Japanese living in Japan. Smoking increases the risk of lung cancer (Dela Cruz et al. 2011). In Norway, where only one-fourth as many cigarettes are smoked per person, rate of lung cancer is five times less than that in Britain. It increased much later in women than in men in whom it increased about 15-fold since 1930, when smoking became prevalent. Skin cancer correlates with excessive exposure to sunlight, especially for races with light skin pigmentation. Similarly, exposure to radiation may frequently give rise to leukemias. The risk of developing cancer can be decreased by avoiding smoking, a calorie and fat-rich diet, and excessive sun and radiation exposure.

3.7 Prevention and Early Detection

A closer insight into the causes of cancer certainly opens ways to prevention. Nevertheless, it cannot be completely eradicated unless the underlying biological complicacies of the disease are fully understood and handled effectively. Significantly effective and less expensive treatment, increased probability of survival, and less morbidity could be ensured to cancer patients if the disease is diagnosed early. Evidence-based prevention strategies can prevent the risk of about 30–50% of cancers. For example, about one million cancer cases per year could be possible to prevent by vaccination against HPV and hepatitis B viruses (Globocan 2018). In this way, early detection and adequate management of patients who develop cancer can cure many types of cancers. However, late-stage or inaccessible diagnosis or treatment is common. New research opens up early detection of various cancers, like mammography and BRCA screening for breast cancer; Pap smear test, which can detect precancerous cell changes of the cervix, has been primarily responsible for a 70% decline in uterine cancer deaths in the USA over the last five decades. In underdeveloped nations and among members of lower socioeconomic groups in developed countries, cervical cancer remains a major cause of female death. The availability of pathology services in public sector was reported from only 26% of low-income countries, which was far less than above 90% of high-income countries, which reported available treatment services. This says of the significant and increasing economic impact of cancer. The total annual economic cost of cancer in 2010 was estimated at approximately US$ 1.16 trillion (Plummer et al. 2016). Only 1 in 5 low- and middle-income countries have the necessary data to drive cancer policy.

3.8 Conclusion

Every cancer type requires a specific treatment regimen in terms of say surgery, radiotherapy, or chemotherapy. Thus, a correct diagnosis is crucial for an adequate and effective treatment. Prior to treatment and management of cancer patients, the goals of such undertakings must be determined and health services should be integrated and be made people-centric. Apart from the primary goal, i.e., to cure cancer or increase the patient's life span, improving the patient's quality of life should also be taken into consideration. For this, supportive or palliative care and psychosocial support are necessary. By early detection and best possible treatment, some of the most common cancer types, such as breast cancer, cervical cancer, oral cancer, and colorectal cancer, could be treated. Appropriate treatment can cure even metastatic conditions like testicular seminoma, leukemias, and lymphomas in children. Palliative care improves the quality of life of patients and their families rather than just curing the symptoms. Palliative care is effective not only for cancer patients but also for patients with other chronic fatal diseases, where there is little chance of cure. It can also relieve more than 90% of advanced-stage cancer patients from physical, psychosocial, and spiritual problems. Community-based and home-based healthcare strategies and palliative care for patients from low-income groups are some effective ways to relieve pain. Terminal phase cancer pain suffered by over 80% of patients could be treated by oral morphine (Howie and Peppercorn 2013).

Cancer has been a major focus of research for decades due to its impact on human health and the hope to develop a cure. On December 23, 1971, US President Richard M. Nixon signed the National Cancer Act to initiate *the war on cancer*. During the last five decades, over 100 billion dollars was sanctioned for the National Cancer Institute for an unprecedented expansion of basic biological research. In the years following the National Cancer Act, improved diagnosis and treatment have increased the five-year survival rate from 50% to 60%. Death rates for childhood cancers and cancers of the stomach, uterus, and colon have dropped dramatically. However, death rates from lymphoma, lung, prostate, liver, and brain cancers have risen markedly. Though these studies have broadened our way toward exploring the cellular and molecular basis of cancer, much success has not been achieved in the prevention or cure of most cancers. Although cancer is still not conquered, many believe that even difficult cancers will come under control with a new generation of diagnostics and treatments based on a detailed understanding of the inner working of tumor cells.

References

Ablashi DV, Chatlynne LG, Whitman JE, Cesarman E (2002) Spectrum of Kaposi's sarcoma-associated herpes virus, or human herpes virus 8, diseases. Clin Microbiol Rev 15(3):439–464

Brady G, MacArthur GJ, Farrell PJ (2007) Epstein–Barr virus and Burkitt lymphoma. J Clin Pathol 60(12):1397–1402

Bray F, Kiemeney L (2017) Epidemiology of prostate cancer in Europe: patterns, trends and determinants. In: Bolla M, van Poppel H (eds) Management of prostate cancer: a multidisciplinary approach. Springer-Verlag, Berlin, pp 1–11

Bray F, Ferlay J, Soerjomataram I, Siegel RL et al (2018) Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 68(6):394–424

Classics in oncology. Sir Percivall Pott (1714 – 1788) (1974) CA Cancer J Clin 24(2):108–116

Cooper GM (2000) The cell: a molecular approach, 2nd edn. Sinauer Associates, Sunderland, MA

Dagenais GR, Leong DP, Rangarajan S, Lanas F et al (2020) Variations in common diseases, hospital admissions, and deaths in middle-aged adults in 21 countries from five continents (PURE): a prospective cohort study. Lancet 395(10226):785–794

Dela Cruz CS, Tanoue LT, Matthay RA (2011) Lung cancer: epidemiology, etiology, and prevention. Clin Chest Med 32(4):605–644

Gallo RC, Blattner WA, Reitz MS, Ito Y (1982) HTLV: the virus of adult T-cell leukemia in Japan and elsewhere. Lancet 1(8273):683

GLOBOCAN (2018) International Agency for Research on Cancer, GLOBOCAN 2018 accessed via Global Cancer Observatory

Hanahan D, Weinberg RA (2000) The hallmarks of cancer. Cell 100(1):57–70

Herrero R, Murillo R (2018) Cervical cancer. In: Thun MJ, Linet MS, Cerhan JR, Haiman CA, Schottenfeld D (eds) Cancer epidemiology and prevention, 4th edn. Oxford University Press, New York, pp 925–946

Howie L, Peppercorn J (2013) Early palliative care in cancer treatment: rationale, evidence and clinical implications. Therap Adv Med Oncol 5(6):318–323

International Agency for Research on Cancer (IARC) (2014) In: Stewart BW, Wild CP (eds) World cancer report 2014. International Agency for Research on Cancer, Lyon

Klug WS, Cummings MR, Spencer CA, Palladino MA (2016) Concepts of genetics, 10th edn. Pearson Education, Limited, India

Kvale R, Myklebust TA, Engholm G, Heinavaara S et al (2017) Prostate and breast cancer in four Nordic countries: a comparison of incidence and mortality trends across countries and age groups 1975–2013. Int J Cancer 141(11):2228–2242

Lin YC, Li L, Makarava AV, Burgers PM et al (2014) Molecular basis of aflatoxin-induced mutagenesis – role of the aflatoxin B1-formamidopyrimidine adduct. Carcinogenesis 35(7): 1461–1468

London WT, Petrick JL, McGlynn KA (2018) Liver cancer. In: Thun MJ, Linet MS, Cerhan JR, Haiman CA, Schottenfeld D (eds) Cancer epidemiology and prevention, 4th edn. Oxford University Press, New York, pp 635–660

Marengo A, Rosso C, Bugianesi E (2016) Liver cancer: connections with obesity, fatty liver, and cirrhosis. Annu Rev Med 67:103–117

Monteiro AN, Waizbort R (2007) The accidental cancer geneticist: hilário de gouvêa and hereditary retinoblastoma. Cancer Biol Ther 6(5):811–813

Plummer M, Franceschi S, Vignat J, Forman D et al (2015) Global burden of gastric cancer attributable to helicobacter pylori. Int J Cancer 136:487–490

Plummer M, de Martel C, Vignat J, Ferlay J et al (2016) Global burden of cancers attributable to infections in 2012: a synthetic analysis. Lancet Glob Health 4(9):e609–e616

Poiesz BJ, Ruscetti FW, Gazdar AF, Bunn PA et al (1980) Detection and isolation of type C retrovirus particles from fresh and cultured lymphocytes of a patient with cutaneous T-cell lymphoma. Proc Natl Acad Sci U S A 77(12):7415–7419

Pott P (1775) Cancer scroti. In: Pott P (ed) Chirurgical observations. L. Hawes, W. Clarke, R Collins, London, pp 179–180

Rubin DC, Shaker A, Levin MS (2012) Chronic intestinal inflammation: inflammatory bowel disease and colitis-associated colon cancer. Front Immunol 3(107):1–10

Varmus H, Unni AM, Lockwood WW (2016) How cancer genomics drives cancer biology: does synthetic lethality explain mutually exclusive oncogenic mutations? Cold Spring Harb Symp Quant Biol 81:247–255

Vogelstein B, Papadopoulos N, Velculescu VE, Zhou S et al (2013) Cancer genome landscapes. Science (New York, N.Y.) 339(6127):1546–1558

Wagener C, Stocking C, Muller O (2017) Cancer signaling: from molecular biology to targeted therapy. Wiley-VCH, Weinheim

Walboomers JM, Jacobs MV, Manos MM, Bosch FX et al (1999) Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. J Pathol 189(1):12–19

Weinberg RA (2014) The biology of cancer, 2nd edn. Garland Science, Taylor & Francis Group, New York

World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) (2018) *Continuous Update Project Report: Diet, Nutrition, Physical Activity and Colorectal Cancer 2016*. World Cancer Research Fund International, London. aicr.org/continuous-up-date-project/reports/colorectal-cancer-2017-report.pdf

Yoshida M, Miyoshi I, Hinuma Y (1982) Isolation and characterization of retrovirus from cell lines of human adult T-cell leukemia and its implication in the disease. Proc Natl Acad Sci U S A 79: 2031–2035