Updating the Definition of Cancer

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ABSTRACT

Most definitions of cancer broadly conform to the current NCI definition: "Cancer is a disease in which some of the body's cells grow uncontrollably and spread to other parts of the body." These definitions tend to describe what cancer "looks like" or "does" but do not describe what cancer "is" or "has become." While reflecting past insights, current definitions have not kept pace with the understanding that the cancer cell is itself transformed and evolving. We propose a revised definition of cancer: Cancer is a disease of uncontrolled proliferation by transformed cells subject to evolution by natural selection. We believe this definition captures the essence of the majority of previous and current definitions. To the simplest definition of cancer as a disease of uncontrolled proliferation of cells, our definition adds in the adjective "transformed" to capture the many tumorigenic processes that cancer cells adopt to metastasize. To the concept of uncontrolled proliferation of transformed cells, our proposed definition then adds "subject to evolution by natural selection." The subject to evolution by natural selection modernizes the definition to include the genetic and epigenetic changes that accumulate within a population of cancer cells that lead to the lethal phenotype. Cancer is a disease of uncontrolled proliferation by transformed cells subject to evolution by natural selection.

Introduction

Most definitions of cancer broadly conform to the current NCI definition: "Cancer is a disease in which some of the body's cells grow uncontrollably and spread to other parts of the body" (see **Table 1**; ref. 1). These definitions tend to describe what cancer "looks like" or "does" but do not describe what cancer "is" or "has become." While reflecting growing and useful insights, current definitions have not kept pace with the understanding that the cancer cell is itself transformed and evolving.

Cancer was first recognized as a growing tissue mass, a tumor (2, 3). They could observe what it looked like, how fast it grew, and how it often appeared to take a "bite" out of the body. The tumors themselves seemed, at times, to spread to other parts of the body and were recognized as fatal. Two things are evident at this stage of understanding. First, it aligns with a disease of abnormal and uncontrolled growth with the capacity to spread. Second, there was no distinction made between the concepts of tumor and cancer. Even today, these terms are often used interchangeably.

The "cellular theory" of disease formulated by Rudolf Virchow in the mid-19th century postulates that all diseases, including cancer, arose from changes in cells. This knowledge led to an understanding of cancer as a disease of abnormal cell proliferation (4). Many writings of the era reflect how cancer was recognized as the product of proliferating cells that form a tumor (5). It was also recognized that cancer cells drive the growth of tumors and eventually their spread as metastases (6). Cancer cells seemed to create or at least reside in tumors. These ideas formed the basis of our current general definitions that characterize cancer as "an uncontrolled growth or proliferation of cells that have the capacity to spread to other parts of the body" (7, 8).

That cancer cells originate from normal cells was an important insight in the mid-20th century. With subsequent advances in molecular biology, it was recognized that cancer cells had undergone a sequence of driver mutations or "hits" leading to uncontrolled proliferation, failure to differentiate, and successful invasion into normal tissue (9–11). Cancer was conceptualized as "a disease of the genes." Within this framework, mutations are largely regarded as fixed triggers and, to a lesser extent, as reflections of selective forces in a dynamically changing population and environment.

Changes in gene frequency within a population are a defining feature of evolution. Cancer, however, is more than just somatic evolution or a population of cells exhibiting genetic heterogeneity. The populations of cancer cells evolve adaptations. The tumor microenvironment favors some phenotypic characteristics of cancer cells over others, and the adaptations of the cancer cells feedback onto their microenvironment. Cancer cells evolve to increase their uptake of resources, co-opt normal cells such as fibroblasts, evade the immune system or recruit protumor components, produce public goods (angiogenesis and aspects of the extra-cellular matrix), and create and tolerate acidic conditions (12–14). Indeed, adaptations of cancer cells that emerge from evolution by natural selection result in many, if not all, of the hallmarks of cancer (15).

The role of natural selection in initiating and driving cancer is alluded to in the definition of cancer hallmarks. Hanahan and Weinberg state that "Tumor development proceeds via a process formally analogous to Darwinian evolution, in which a succession of genetic changes, each conferring one or another type of growth advantage, leads to the progressive conversion of normal human cells into cancer cells." (15, 16). It is now clear that cancer cells must also continue to evolve within a cancer in response to selective pressures such as changes in blood flow and host immune response (17). It is this evolution by natural selection that eventually results in adapted cancer cells that are resistant to drug and radiation therapies—ultimately, the evolution of resistance by natural selection explains the near certainty of death from late-stage cancers (18).

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Mol Cancer Res 2023;21:1142–7

doi: 10.1158/1541-7786.MCR-23-0411

Table 1. Select definitions of cancer.

Definition of cancer	Source	Date
In medicine, a roundish, hard, unequal, scirrhous tumor of the glands, which usually ulcerates, is very painful, and generally fatal.	An American Dictionary of the English Language. (Webster) (35)	1828
A tumor is a new growth of tissue which apparently originates and grows spontaneously, possesses an atypical architecture, does not subserve the uses of the organism, and reaches no definite termination of growth.	Textbook of General Pathological Anatomy and Pathogenesis (Ziegler) (36)	1898
A malignant tumour eating the part it is in, spreading indefinitely, & recurring when removed.	Oxford Dictionary (37)	1919
A tumor is an autonomous new growth of tissue.	Neoplastic Disease – a treatise on tumors (Ewing) (38)	1919
Cancer is a disease in which some of the body's cells grow uncontrollably and spread to other parts of the body.	National Cancer Institute (1)	2023
Cancer isn't a single disease. Cancer is a group of diseases characterized by the uncontrolled proliferation of cells. Ignoring the body's signal to stop, malignant cells multiply to form tumors in organs and tissues or, in the case of blood cancers, crowd out normal cells in the blood stream and bone marrow.	American Association for Cancer Research (7)	2023
Cancer is when abnormal cells divide in an uncontrolled way. Some cancers may eventually spread into other tissues.	Cancer Research UK (39)	2023
A group of diseases in which cells in the body change and grow out of control. Most types of cancer cells form a lump, or mass called a tumor.	American Cancer Society (8)	2023
Cancer is a generic term for a large group of diseases that can affect any part of the body. Other terms used are malignant tumours and neoplasms. One defining feature of cancer is the rapid creation of abnormal cells that grow beyond their usual boundaries, and which can then invade adjoining parts of the body and spread to other organs; the latter process is referred to as metastasis. Widespread metastases are the primary cause of death from cancer.	World Health Organization (20)	2023
Cancer refers to diseases in which abnormal cells divide out of control and are able to invade other tissues. Cancer cells can spread to other parts of the body through the blood and lymph systems, which help the body get rid of toxins.	Centers for Disease Control and Prevention (40)	2023
A malignant tumor of potentially unlimited growth that expands locally by invasion and systemically by metastasis	Merriam-Webster Medical Dictionary - online (41)	2023
A malignant neoplasm (including both carcinoma and sarcoma) which arises from the abnormal and uncontrolled division of cells and which invades and destroys the surrounding tissues.	Oxford Reference - online (42)	2023
A group of diseases in which abnormal cells grow in an uncontrolled way, sometimes forming tumors.	Harvard Medical Dictionary of Health Terms - online (43)	2023
A cancer is an abnormal growth of cells (usually derived from a single abnormal cell). The cells have lost normal control mechanisms and thus are able to multiply continuously, invade nearby tissues, migrate to distant parts of the body, and promote the growth of new blood vessels from which the cells derive nutrients.	Merck Manuals - online (44)	2023
Cancer is a group of diseases involving abnormal cell growth with the potential to invade or spread to other parts of the body.	Wikipedia - online (45)	2023

An updated definition of cancer should include the force of natural selection acting on the initiation and progression of the cancer cell populations. We propose an updated definition: *Cancer is a disease of uncontrolled proliferation by transformed cells subject to evolution by natural selection*. In what follows, we will elaborate on the details associated with the central words of this definition. We will conclude by discussing why updating the definition matters for understanding, conceptualizing, and treating cancer.

Terms contributing to the definition "cancer is a disease of uncontrolled proliferation by transformed cells subject to evolution by natural selection."

Disease

Disease is a term used to describe a state of illness or abnormality that represents a disruption of the normal physiologic functioning of an organism. Diseases can arise from a wide range of factors, including pathogens (e.g., bacteria, viruses, parasites), genetic mutations, environmental factors, and lifestyle. Diseases not only negatively affect an individual's physical well-being but also have profound social, psychologic, and economic implications.

Cancer is a disease because the cancer cells' growth, spread, resource use and metabolite production, tissue disruption, and co-option of normal noncancerous cells disrupt normal bodily functions, ultimately causing pain, organ failures, and cancer-related syndromes such as cachexia. Cancer not only destroys a person's body but also profoundly affects a person's mental health and negatively impacts the people around them, disrupting families and friendships. Cancer as a disease kills 10 million people per year globally, reflecting how common and lethal it remains (19). The economic impact of cancer is immense, including direct medical costs, lost productivity due to illness and premature death, and the emotional and psychologic effects on patients and their families. The cost of cancer to the world exceeds 1 trillion dollars per year (19).

Many of the current definitions of cancer refer to cancer as a collection of diseases because cancer arises in many different organs and is sometimes stratified by tissue-specific genetic hits (oncogenes,

e.g., BRAF). For example, the WHO describes cancer as "a generic term for a large group of diseases that can start in almost any organ or tissue of the body" (20). Given the cellular origin of cancer and the convergent nature of how cancer evolves and spreads through all individuals, to refer to cancer as a group of diseases is unnecessary. In contrast, we generally do not refer to malaria or influenza as a group of diseases. These diseases are simply "malaria" and the "flu" despite their diverse variants.

Uncontrolled Cell Proliferation

Uncontrolled cell proliferation has been at the core of the original sense of cancer going back millennia. This is also consistent with pre-evolution perspectives of cancer in the 18th, 19th, and much of the 20th century that emerged after cells were initially identified. Cell proliferation in multicellular organisms is tightly controlled. Most cells of a mammal—and therefore a human patient—have limits on the possible number of cell divisions (21). Differentiated somatic cells differentiate into their fate, tissue, and organ and thereafter lose their ability for continued cell division. For the most part, any deviation from this trajectory results in programmed cell death (apoptosis). The body's stem cells or progenitor cells have a kind of replicative immortality. They are subject to highly regulated tissue control mechanisms that dictate when they divide and, to a certain extent, whether they divide symmetrically (producing another stem cell) or, more often, asymmetrically (producing a daughter cell while preserving themselves). The daughter cell of a stem cell will undergo a relatively fixed number of cell divisions while differentiating into a non-proliferative fate. These cells serve the maintained structure and function (i.e., homeostasis) of the organ and the whole organism. In this sense, proliferation is a tightly controlled whole organism function. The hierarchical organization of tissue maintenance and even the decreasing rate of cell divisions of differentiating cells appear to have minimized somatic evolution in a way that contributes to the success of animals (22).

Uncontrolled

A simple definition of cancer—that its growth or proliferation is "uncontrolled"—requires a specification of what component or extent is uncontrolled. Generally, the term uncontrolled refers to something that lacks proper regulation, management, or restraint. Uncontrolled implies that a process or situation is not being controlled in a way to maintain stability, order, or predictability. At the tissue level, uncontrolled implies that the normal mechanisms or systems designed to govern a process or maintain homeostasis are not functioning as is typical, leading to undesirable or potentially harmful outcomes. Although normal cells grow (or not), divide (or not), differentiate (or not), and die in a regulated manner, cancer cells no longer require contact with other cells or a defined function in the tissue to stay alive. The many mechanisms by which cancer cells avoid apoptosis reflect their avoidance of multiple pro-apoptotic cues. Therefore, the proliferation of cancer cells is out of the control of the tissue and of its neighbor cells.

Independence from the cues that induce cell death, however, does not mean that cancer cell proliferation is free from limitations. Like any growing population, there are limits to population growth imposed by limitations of resources, space, habitat degradation, and accumulation of hazards. In this way, the "uncontrolled" proliferation of cancer cells is regulated not by tissue control mechanisms but by environmental limits to growth. Typically, normal cells are homeostatically maintained at densities and numbers that leave them with sufficient access to resources, reasonable crowding, or limited exposure to metabolites that can be toxic. A growing population of cancer cells becomes limited by famine, space, and toxicity balance. Thus, their proliferation and mortality rates are not regulated by homeostatic controls but rather by ecological parameters (including physical, chemical, and biological). This control is similar to how populations of unicellular organisms on the ocean floor are limited by space, nutrients, and competition. Rather than normal tissues, cancer cell populations become packed at much higher densities (lumps or tumors). As noted in the 1828 Webster's Dictionary definition of cancer: "In medicine, a roundish, hard, unequal, scirrhous [hard and fibrous] tumor of the glands, which usually ulcerates, is very painful, and generally fatal." Uncontrolled proliferation leads to densely packed cancer cells regulated by standard ecologically-imposed limits to growth.

Proliferation

Proliferation refers to an increase, growth, or multiplication in the number or quantity of something. Proliferation generally implies a fast and sometimes uncontrollable expansion or growth of the subject in question. In biology, proliferation describes the process of cell division, leading to an increase in the number of cells or organisms in a population. However, there are two sides to population growth: births (proliferation) and deaths (cell mortality rate). Net proliferation rates of single-cell organisms and cells of an animal, including cancer, can be defined as proliferation rate minus mortality rate. In a growing tumor, there generally are increases in both cell proliferation and cell death. For cancer cells, uncontrolled proliferation means that under ideal conditions, cancer cells have proliferation rates that far exceed their death rates. In the absence of density-dependent feedback (limits to growth), the population of cancer cells, like any organism, will grow exponentially.

Transformed Cells

Every time a cell divides within a multicellular organism such as a human, the whole organism plays with evolutionary fire (23–25). For any animal, the individual cells contribute to the survival and proliferation of the whole organism. In other words, the animal is the organism, not the individual constituent cell. It is within this population of constituent cells that cancer originates. For cancer initiation, three things seem necessary and perhaps sufficient: (1) long runs of cell division, (2) accumulation of oncogenic genetic and epigenetic mutations, and (3) a permissive tissue environment that does not block these long runs of cell division or the persistence of increasingly aberrant cells (25). Note that we have changed the common definition preposition "' of' transformed cells" to "' by' transformed cells." Although "of" refers to a characteristic of something, "by" indicates the performer of an action. In this case, the transformed cells perform the action of uncontrolled proliferation.

Transformed

Transform means to undergo a significant and often radical change in appearance, form, or character. When something is transformed, it has been altered or converted from its original state into a new one, usually with different properties, appearance, or functions. Transformation is a process of change, of metamorphosis. Transformation is a process central to the formation of cancer cells, allowing them to become uncoupled from the regulatory mechanisms of their non-transformed ancestor.

When applied to cancer cells, transformation refers to the process by which normal cells acquire genetic and epigenetic alterations that lead them to become malignant. These transformations by genetic and

epigenetic alterations are best summarized by Hanahan and Weinberg's "Hallmarks of Cancer" (15). Inclusion of the term "transformed" in the definition implies the presence of all of the currently-defined hallmarks of cancer plus those yet to be discovered. Many current cancer definitions, including the NCI, for example, include "spreading" as a key component (1). Rather than naming the single hallmark of metastasis, the term "transformed" is inclusive of all of the hallmarks.

The cancer cells are also "transformed" by shifting between levels of selection. The initiating cancer cells shift from being part of the whole organism (i.e., a unit of selection among its population and environment) to become its own unit of selection (among its population and environment; refs. 26, 27).

Cells

A cell is a structural and functional unit of life that carries out the essential processes that define living organisms. Cells form the basis of all living and independently replicating organisms on Earth, from single-celled organisms like bacteria to multicellular organisms like plants and animals. Cells in the body exist as part of multicellular units: tissues, vasculature, and organs. It is worth noting that in unicellular eukaryotes, a species is defined and recognized by genetic separation from other cells and by phenotypic differences. Because cancer cells have altered genomes as well as observable physical differences from normal human cells, Julian Huxley in 1956 was the first to "deduce that carcinogenesis may be a form of speciation" (28). Both cancer initiation and the continued adaptations of cancer cells as the disease progresses can be recognized as a speciation process. A cancer cell gains autonomy and exists as a unicellular entity that survives and can be selected for independently of the constraints of its multicellular host tissue of origin (18, 28–30). The cancer cell becomes the unit of selection.

Subject

When used as a verb, "subject" means to cause someone or something to undergo or experience a particular treatment, situation, or condition. The verb form is usually followed by the preposition "to," as in "subjecting a species to a stressful environment." A cancer cell is a unit that is "subject to" the laws of evolution.

Evolution

Evolution in biological systems is defined as the change in the heritable characteristics of a population over generations. It provides a unifying theory of biology that connects the diversity of life on Earth, as well as the shared ancestry of all organisms. Forces of evolution include mutation, genetic drift, gene flow, and natural selection. The recipe of inheritance means that the offspring resembles the parent but with heritable variation. During the Golden Age of population genetics and with the rediscovery of Mendel's Laws, there was faith in the hypothesis that particular genes translated directly into phenotypes and that novel heritable variation resulted from mutations of genes resulting in new alleles. This simple picture changed rapidly with knowledge of how one gene can influence unrelated phenotypic traits (pleiotropy) and how the effect of one mutation can be dependent on another mutation (epistasis). Since then and with molecular biology, new sources and means of generating heritable variation have been appreciated. In particular, cancer biology has expanded our understanding of the generation of heritable variation to include anything from genetic mutations, epigenetic alterations, chromosomal instabilities, aneuploidies, to copy-number variations. Mutations occur frequently in normal animal cells leading to "somatic evolution." This somatic evolution is generally manifested as mutations and genetic drift. Many of these mutations lead to the death of the cell, but some, subject to natural selection, can lead to cancer. Evolution, therefore, can occur in any cell population of an organism, but this does not necessarily lead to cancer. Cancer initiation and progression are ultimately driven by the force of natural selection on accumulating mutations and heritable changes. Natural selection acting on the cells of an animal is a unique and universal characteristic of cancer.

Natural Selection

Natural selection is the force of evolution that promotes adaptations or adaptedness. Adaptations are heritable traits that maximize fitness given the particular circumstances, and adaptedness can be seen as heritable traits that confer higher fitness than other possible traits given the circumstances. Fitness is defined as the per capita growth rate (i.e., birth rate minus death rate). For cancer cells, therefore, fitness is defined as net proliferation rate (i.e., proliferation rate minus mortality rate). For natural selection to occur, there must be heritable variation (whether genetic, epigenetic, chromosomal, copy-number variation, etc.), a competition to survive, and the heritable variation must influence the success of the struggle. Cancer exhibits all of these properties (heritable variation, struggle, and that these are linked) that are necessary and sufficient for natural selection. If cancer did not exhibit these properties, cancer would not evolve resistance or any number of other adaptations associated with its hallmarks. Hence, evolution and, more specifically, evolution by natural selection is a defining characteristic of cancer. This characteristic of cancer needs to be included (explicitly or implicitly) in any definition of cancer since natural selection is the process that influences the success of the cancer itself.

Heritable variation

A range of genetic variation for different traits is present within any population of organism. This variation arises from mutations, genetic recombination during reproduction, drift, gene flow between populations, and all the various mechanisms that generate heritable variation. This variation means that the offspring is similar to the parent but not entirely identical. Deviations in the constitution of offspring are not so large as seeing a giraffe beget a sloth. The deviations are also large and persistent enough to see the emergence of, for example, varieties of domestic dogs, all owing their ancestry to wolves. In cancer, it is clear that genetic, epigenetic, and chromosomal heterogeneities exist. These deviations have been described among cancer cells of a tumor, among tumors of the same patient, among patients with the same cancer type, and among different cancer types. This genetic variation lays a fundamental "fuel" for natural selection in cancers.

Struggle for survival

The struggle for existence recognizes that organisms can produce more offspring than can be supported by their circumstances, called a Malthusian Principle (31–33). Ecologically, the struggle for survival emerges from the fact that all populations of organisms have the capacity to grow exponentially under ideal conditions. Yet, no population can grow exponentially forever. There are limits to growth. Although the "uncontrolled" proliferation of cancer cells recognizes how they have broken free of whole organism control, they must compete with each other and struggle to survive growth constraints as

they compete for resources and space and suffer toxic and immune hazards.

Heritable variation influences the struggle

The environment exerts selection pressures on populations, favoring the survival and reproduction of individuals with certain traits. This pressure can be stabilizing, directional, or disruptive, depending on the specific environmental conditions and the range of variation in the population. In the context of cancer, the selection pressure comes from the microenvironment and ecological parameters. For example, ecological parameters (physical, chemical, or biological) can be the availability of nutrients, oxidants, space, and interactions with other cancer cells or with normal cells, including immune cells. The selection pressure exerted by the environment can favor the survival and proliferation of cells with certain characteristics, such as those that can resist apoptosis or evade the immune system.

Some individuals in a population may be better adapted to their environment than others due to their particular genetic traits. These individuals are more likely to survive, reproduce, and pass on their advantageous traits to their offspring (i.e., inheritance). These individuals also compete with each other and with normal cells for limited resources, such as nutrients and space, especially as the number of cancer cells increases. This competition drives further selection for cells with more aggressive characteristics, for example, with increased metabolism, promotion of angiogenesis, more rapid nutrient uptake, or invasion and metastasis (15). Cells that have acquired genetic changes conferring a growth or survival advantage are more likely to proliferate and pass on these traits to their offspring (progeny). Over time, this leads to the expansion of the population of cells carrying these advantageous traits.

Therefore, populations become better adapted to their environment as a result of natural selection. The adaptation can lead to changes in the frequency of specific traits within the population and, in some cases, the emergence of new phenotypes of cancer. This line of events is similar to the emergence of Darwin's finches but, in cancer, defined by how they fill distinct ecological niches provided by the tumor (34). Moreover, as the tumor grows and evolves, different subpopulations of cancer cells may adapt to different niches within the tumor microenvironment. This differential adaptation lead to the development of intratumoral heterogeneity that can further contribute to cancer progression and therapeutic resistance.

Why a Revised Definition Matters

We propose a revised definition of cancer: Cancer is a disease of uncontrolled proliferation by transformed cells subject to evolution by natural selection.

We believe this definition captures the essence of the majority of previous and current definitions. To the simplest definition of cancer as a *disease* of uncontrolled proliferation of cells, our definition adds in the adjective "transformed" to capture the many processes that cancer cells adopt to demonstrate its observed Hallmarks of Cancer, including the ability to invade host organs and metastasize. To the concept of uncontrolled proliferation of transformed cells, our proposed definition then adds "subject to evolution by natural selection." The subject to evolution by natural selection modernizes the definition to include the genetic and epigenetic changes that accumulate within a population of cancer cells that lead to the lethal phenotype. Importantly, it takes the mystery out of cumulative mutations and explains how the cancer cell population evolves by predictable evolutionary principles to a lethal phenotype. All of the necessary processes for evolution by natural selection—heritable variation, a struggle for existence, and variation influencing this struggle—are well-documented features in cancer, even if not described in exactly these terms. Cancer, therefore, can be viewed as a process of evolution by natural selection, where the cancer cell is the unit of selection. The genetic changes and selective pressures within the tumor microenvironment drive the development of cancer cells with potentially increasingly aggressive and malignant characteristics that ultimately result in the death of the host patient. Understanding that cancer cells are actually following the principles of natural selection codifies how cancer changes over time and opens opportunities for developing optimal diagnostic and interventional strategies.

Authors' Disclosures

S.R. Amend reports grants from CDMRP/PCRP, CDMRP/PCRP, and Prostate Cancer Foundation during the conduct of the study; other support from Keystone Biopharma, Inc. outside the submitted work. E.U. Hammarlund reports grants from The Swedish Science Council and The Crafoord Foundation during the conduct of the study. K.J. Pienta reports grants from NCI and Prostate Cancer Foundation during the conduct of the study; personal fees from Cue Biopharma; other support from Keystone Biopharma, Peal Therapeutics, and O'Traces, Inc. outside the submitted work. No disclosures were reported by the other authors.

Acknowledgments

The authors gratefully acknowledge support from the Prostate Cancer Foundation (to S.R. Amend, K.J. Pienta), the NCI (CA093900, U54CA143803, P50CA058236 to K. J. Pienta; 1R01CA258089 to J.S. Brown), the U.S. Department of Defense (W81XWH-20–10353, W81XWH- 22–1-0680 to S.R. Amend), the National Science Foundation (PHY-1659940, PHY-1734030 to R.H. Austin), the Crafoord Foundation (20220633 to E.U. Hammarlund), the Swedish Research Council (2019–05254 to E.U. Hammarlund), and the Patrick C. Walsh Prostate Cancer Research Fund to S.R. Amend.

Received May 25, 2023; revised June 28, 2023; accepted June 29, 2023; published first July 6, 2023.

References

1. National Cancer Institute. What is cancer? Available from: https://www.cancer.gov/about-cancer/understanding/what-is-cancer.
2. Ghallioungui P. Magic and medical science in ancient Egypt. (Barnes & Noble, 1965).
3. Hajdu SI. A note from history: landmarks in history of cancer, part 1. Cancer 2011;117:1097–102.
4. Hirschwald A. Berlin, Germany, 1858.
5. Hajdu SI. A note from history: landmarks in history of cancer, part 3. Cancer 2012;118:1155–68.
6. Paget S. The distribution of secondary growths in cancer of the breast. 1889. Cancer Metastasis Rev 1989;8:98–101.
7. American Association for Cancer Research. What is cancer? Available from: https://www.aacr.org/patients-caregivers/about-cancer/what-is-cancer/.
8. American Cancer Society. Cancer glossary: definitions & phonetic pronunciations. Available from: https://www.cancer.org/cancer/understanding-cancer/glossary.html#alpha-c.
9. Lipsick J. A history of cancer research: tumor suppressor genes. Cold Spring Harb Perspect Biol 2020;12:a035907.
10. Vogelstein B, Papadopoulos N, Velculescu VE, Zhou S, Diaz LA Jr, Kinzler KW. Cancer genome landscapes. Science 2013;339:1546–58.

11. Rane JK, Frankell AM, Weeden CE, Swanton C. Clonal evolution in healthy and premalignant tissues: implications for early cancer interception strategies. Cancer Prev Res 2023;16:369–78.
12. Maley CC, Aktipis A, Graham TA, Sottoriva A, Boddy AM, Janiszewska M, et al. Classifying the evolutionary and ecological features of neoplasms. Nat Rev Cancer 2017;17:605–19.
13. Gillies RJ, Verduzco D, Gatenby RA. Evolutionary dynamics of carcinogenesis and why targeted therapy does not work. Nat Rev Cancer 2012;12: 487–93.
14. Aguade-Gorgorio G, Kauffman S, Sole R. Transition therapy: tackling the ecology of tumor phenotypic plasticity. Bull Math Biol 2021;84:24.
15. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell 2011; 144:646–74
16. Hanahan D, Weinberg RA. The hallmarks of cancer. Cell 2000;100:57–70.
17. Somarelli JA. The hallmarks of cancer as ecologically driven phenotypes. Front Ecol Evol 2021;9:661583.
18. Pienta KJ, Hammarlund EU, Brown JS, Amend SR. The cancer clade, hyperspeciation, evolving evolvability, and the origins of lethal cancer. Mol Cancer Res 2020.
19. Chen S, Cao Z, Prettner K, Kuhn M, Yang J, Jiao L, et al. Estimates and projections of the global economic cost of 29 cancers in 204 countries and territories from 2020 to 2050. JAMA Oncol 2023;9:465–72.
20. World Health Organization. Health topics: cancer. Available from: https://www.who.int/health-topics/cancer#tab=tab_1.
21. Liu J, Wang L, Wang Z, Liu JP. Roles of telomere biology in cell senescence, replicative and chronological ageing. Cells 2019;8:54.
22. Derenyi I, Szollosi GJ. Hierarchical tissue organization as a general mechanism to limit the accumulation of somatic mutations. Nat Commun 2017;8: 14545.
23. Gatenby RA, Gillies RJ, Brown JS. Evolutionary dynamics of cancer prevention. Nat Rev Cancer 2010;10:526–7.
24. Greaves MF. Cancer: the evolutionary legacy. Oxford University Press, 2001.
25. Gatenby RA, Avdieiev S, Tsai KY, Brown JS. Integrating genetic and nongenetic drivers of somatic evolution during carcinogenesis: the biplane model. Evol Appl 2020;13:1651–9.
26. Gatenby RA, Brown J. Mutations, evolution and the central role of a self-defined fitness function in the initiation and progression of cancer. Biochim Biophys Acta Rev Cancer 2017;1867:162–6.
27. Okasha S. Cancer and the Levels of Selection. The British Journal for the Philosophy of Science. In Press; 2023.
28. Huxley J. Cancer biology: comparative and genetic. Biol Rev 1956;31: 474–514
29. Duesberg P, Rausch C, Rasnick D, Hehlmann R. Genetic instability of cancer cells is proportional to their degree of aneuploidy. Proc Natl Acad Sci U S A 1998;95: 13692–7.
30. Vincent TL, Cohen Y, Brown JS. Evolution via strategy dynamics. Theor Popul Biol 1993;44:149–76.
31. Malthus TR. An essay on the principle of population, as it affects the future improvement of society. With remarks on the speculations of Mr. Godwin, M. Condorcet and other writers. (J. Johnson, 1798).
32. Reynolds BA, Oli MW, Oli MK. Eco-oncology: applying ecological principles to understand and manage cancer. Ecol Evol 2020;10:8538–53.
33. Pienta KJ, McGregor N, Axelrod R, Axelrod DE. Ecological therapy for cancer: defining tumors using an ecosystem paradigm suggests new opportunities for novel cancer treatments. Transl Oncol 2008;1:158–64.
34. Darwin C. On the origin of species by means of natural selection, or preservation of favoured races in the struggle for life. (John Murray, 1859).
35. Webster N. An American dictionary of the English language. (S. Converse, 1928).
36. Ziegler E. Lehrbuch der allgemeinen pathologischen Anatomie und Pathogenese. (J.F. Bergmann, 1898).
37. The Oxford English dictionary. (Clarendon Press, 1919).
38. Ewing J. Neoplastic disease - a treatise on tumors. (W.B. Saunders, 1928).
39. Cancer Research UK. What is cancer? Available from: https://www.cancerresearchuk.org/about-cancer/what-is-cancer.
40. Centers for Disease Control and Prevention. Smoking & tobacco use: cancer: what is cancer? Availabe from: https://www.cdc.gov/tobacco/basic_information/health_effects/cancer/index.htm.
41. Merriam-Webster. Dictionary. Cancer definition. Available from: https://www.merriam-webster.com/dictionary/cancer#:~:text=%3A%20a%20malignant%20tumor%20of%20potentially, i. a. s. b. m.
42. Oxford Reference. Overview: cancer. Available from: https://www.oxfordreference.com/display/10.1093/oi/authority.20110803095545897;jsessionid=2D2452E5DC01216DF9948DD4E7AF9F3E.
43. Harvard Health Publishing, Harvard Medical School. Medical dictionary of health terms: A-C. 2011 Dec 13. Available from: https://www.health.harvard.edu/a-through-c#C-terms.
44. Gale RP. Merck Manual. Overview of cancer. 2022 Oct. Available from: https://www.merckmanuals.com/home/cancer/overview-of-cancer/overview-of-cancer#:~:text=A%20cancer%20is%20an%20abnormal, w. t. c. d. n.
45. Wikipedia. Cancer. Available from: https://en.wikipedia.org/wiki/Cancer.