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# Triumph or tragedy: progress in cancer

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**Abstract:** Cancer is probably the number one research area among all human endeavors, receiving the largest portion of science funding in most countries. This is because cancer remains one of the oldest conundrums among all human maladies. Although we now have a greater understanding of the biological and molecular basis of cancer, its diagnosis and therapy still pose great challenges. In this review, our aim is not to establish a comprehensive understanding of cancer, which is essentially impossible, but to outline, in a more provocative way, why cancer research in the pursuit of a cure did not live up to its promise, as the death rate from cancer has not changed much after almost half a century. In addition, we discuss some future perspectives to give some insight into cancer research and debunk the old view that pouring money into cancer research is the only way to overcome this dreadful disease.

**Key words:** Cancer, cancer research, cancer statistics, progress in cancer, cancer publications

## 1. Introduction

The term 'carcinos', meaning 'cancer', was first used by Hippocrates (460–370 BC) long before the terms 'biology', 'chemistry', or 'physics' were around. The causes of this disease have puzzled researchers and practitioners from the earliest times to date. Today, there is no single metabolic pathway or signal transduction network that cancer has not been associated with. Cancer is regarded as a group of complex genetic disorders resulting from mutations at multiple genetic loci and discovery of an ever-increasing number of cancer genes is opening up new scenarios in cancer genetics. Since the discovery of the first tumor-causing viral RAS genes 50 years ago (Harvey, 1964) and their human analogs (i.e. *HRAS*, *NRAS*) more than 30 years ago (Der et al., 1982; Parada et al., 1982), new cancer genes are discovered steadily (Vogelstein et al., 2013; Lawrence et al., 2014). In just a decade, the number of cancer genes discovered increased from 291 to 523 (Futreal et al., 2004).

Today, there are 280 cancer research centers and institutes in the world; of these, 68 are National Cancer Institute (NCI) designated cancer centers in the United States. They have significant budgets dedicated to research in the development of more effective approaches to prevention, diagnosis, and treatment of cancer (http://www.cancerindex.org/clinks1.htm). According to the International Agency for Research on Cancer (IARC), the estimated total annual economic cost of cancer was approximately US$ 1.16 trillion in 2010, the equivalent of more than 2% of the total global gross domestic product.

For the scientific world, cancer research has been a win-win situation. Today, the number of publications made, grants earned, and funds allocated in cancer research far exceed any other scientific endeavors. In the last decade, the number of articles with the term "cancer" in the title increased almost 3-fold (Figures 1 and 2). As of May 2014, the Thomson Reuters Science Citation Index Expanded covered 8636 science journals, 275 of which are classified as "cancer journals" (more than 3% of all journals). Of these cancer journals, 90 had "cancer" as part of the title. This is most probably the trend for books and budgets on cancer.

Despite the extent of research and resources devoted to cancer, it remains one of the most common deadly diseases. In most societies, about 20% of all deaths are from cancer, second only to cardiovascular diseases. The GLOBOCAN project of IARC, which provides estimates for the incidence, mortality, and prevalence of cancer for 184 countries, shows that the incidence of cancer increased from 12.7 million in 2008 to 14.1 million in 2012. This trend is projected to continue and bring the number of cancer cases close to 25 million over the next 2 decades (Ferlay et al., 2010). In the NCI's SEER*Stat database, which provides information on cancer statistics in the USA, the estimates for new cases of cancer and cancer deaths in

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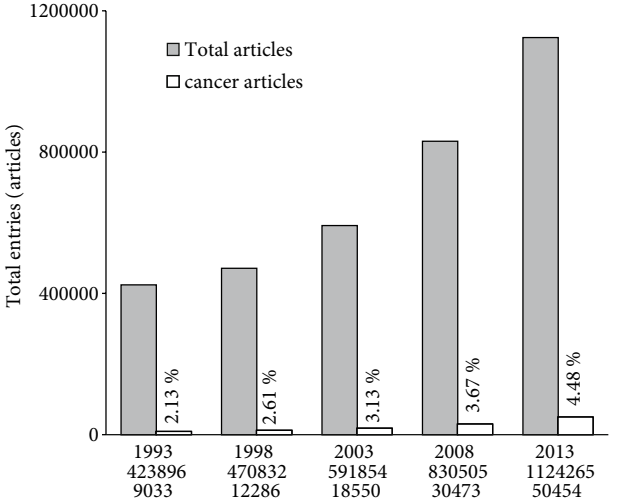



**Figure 1.** The ratio of articles with the term "cancer" in their titles to all articles in PubMed (Medline). Data were compiled online (http://dan.corlan.net/medline-trend.html).

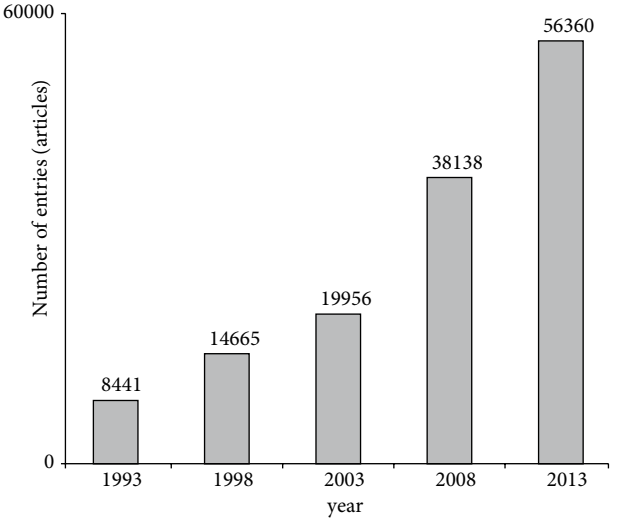



**Figure 2.** The number of articles with the term "cancer" in their titles. Data were compiled from the Science Citation Index Expanded (http://thomsonreuters.com/science-citation-index-expanded/). This index gives no information about the total number of publications recorded for each year.

2014 are 1,665,540 and 585,720, respectively. Cancer in Turkey, like in most other countries, is the second-highest cause of death, just after cardiovascular deaths. However, knowledge of cancer epidemiology in Turkey is still in its infancy, as most health providers did not require a correlative data for cancer registries until recently. The 2014 projections of the Ministry of Health of Turkey for the number of people with cancer and cancer deaths are about 150,000 (207/100,000) and 60,000, respectively.

The signing of the National Cancer Act of 1971 by President Richard Nixon is generally viewed as the beginning of the war on cancer (US Senate, 1971). In his 'State of the Union' address, Nixon declared that "the time has come in America when the same kind of concentrated effort that split the atom and took man to the moon should be turned toward conquering this dread disease". About 30 years later, at the Human Genome Announcement in 2000, President Clinton ventured that "it is now conceivable that our children's children will know the term cancer only as a constellation of stars".

Decades have passed since these declarations and statements on cancer. Their prophecy remains unfulfilled and cancer research has yet to live up to its promise. Cancer, time and again, proves that it is one of the most challenging and least understood of all human maladies, even harder than cracking the atom or putting man on the moon.

**2. What makes cancer so different from other diseases?**

As the title ("Cancer: normal cells' reply to a deadly fate") of this special issue of the Turkish Journal of Biology rightly suggests, for a normal cell destined to die, given the accumulation of all kinds of defects over its lifetime, turning to a cancerous state is a salvation at the expense of the host (i.e. the organism). In other words, turning cancerous is an intrinsic property of cells and is a defense and survival mechanism for the cells under threat. Though it can result in host mortality, cancer is a favorable state for the cells as it allows them a growth advantage and near immortality.

Contrary to many other common diseases, cancer is generally not caused by a single cause such as a pathogen or even, in most cases, a single gene. Most human diseases are caused either by a single gene affecting a specific tissue or by exogenous sources (e.g., infectious agents), both of which can be specifically targeted for potential treatment. This is why some cancers can be prevented (e.g., cervical cancers and some liver cancers) through vaccination against their causative agents (i.e. the human papilloma virus and hepatitis B virus) (Carlos et al., 2010). Conversely, cancer is a disease of all tissues or organs, resulting from endogenously and selectively produced clones of cells, as discussed below. Like normal cells, cancer cells are no foreigners to the organism.

Cancer is a remarkably complex heterogeneous collection of diseases. Recent studies show that even a single tumor has phenotypic variability among its cells and that there is significant genomic heterogeneity between histologically similar tumors (Gerlinger, 2012; Swanton, 2012). This heterogeneity reflects the action of the twin evolutionary forces of variation generation and selection, contributing to the fast-evolving characteristics of cancer

cells (Yates and Campbell, 2012). Due to the harm done to the cell's own repair mechanism, cancer genomes are riddled with mutations. Once the protective shield of cells is harmed (e.g., DNA repair genes), genomes accumulate more and more mutations and the interior and the exterior of cells are in a shambles. It is these mutations that wreak havoc in the cellular machinery, leading cancer cells to confer oncogenic properties such as growth advantage, tissue invasion and metastasis, angiogenesis, and evasion of apoptosis (International Cancer Genome Consortium et al., 2010). Each cancer is characterized by numerous somatic mutations. Some are called "drivers" and cluster within cancer genes, while others are called "passengers" and are more or less randomly distributed. While drivers are the cause of cancer, passengers, which outnumber drivers, are thought to be the consequence of cancer.

In a hypermutated genome, a characteristic of many cancer genomes, determining which mutations are the cause and which mutations are the consequence of cancer is challenging. It is reported that most cancers arise from cells having 2 to 8 driver gene mutations, the remaining being passengers that confer no selective growth advantage (Vogelstein et al., 2013). Although identification of all the altered genes in a tumor is not a difficult task today thanks to high-tech sequencing technologies and bioinformatics tools (International Cancer Genome Consortium et al., 2010), assigning the exact roles of drivers and passengers still remains elusive. Studies showed that some passenger mutations could turn into drivers during tumorigenesis. Mutations in a wide range of genes cause chromosomal instability by as of yet undefined mechanisms that play roles in the cancer cell genome's numeric (aneuploidy) or structural character (Yates and Campbell, 2012). It is now well established that aneuploidy is the main driver of the chaotic state of cancer cells, resulting in rampant disorder not only in genomes but also in a myriad of molecular inventories and reaction repertoires.

There are about 200 different types of cancers, a number close to the number of cell types (or tissues) in the human body (Ferrari, 2013). No other disease can even come close to this variability. Although different cancer cells share similar basic characteristics, such as the ability to reproduce vigorously, each type of cancer is unique with its own causes and consequences. One of the biggest enigmas in cancer research is how cancer cells from a specific tissue or organ can find a niche in their new environment (i.e. in the new tissue) after a long metastatic travel. We know that each of the almost 200 tissues in the human body is composed of its distinct cells with the same genome but different sets of proteins, metabolites, metabolic requirements, and so on. How a metastatic cancer cell parasitizes a different tissue and eventually invades it is still a mystery.

Just a we communicate by language, the language of cells is touch. Each of a myriad of intra- and intercellular molecules plays its role by touching a plethora of others, relaying information to the respective destinations. All these touch and transfer interactions over long-distance pathways in a crowded milieu are intricately regulated in normal cells. In other words, molecular talk is highly regulated and specific in normal cells. In cancer cells, however, this process is loose due to hypermutated genes and thus changes in coding and noncoding RNA transcripts. The defects in proteins and other molecules in a cancer cell cause unprecedented and deregulated molecular touch and transfer. Thus, contrary to a normal cell in which information flow is highly specified over long distances, a cancer cell is in complete disarray with its fragmented information flow, endowing it with multiple selective advantages. It is this redundancy in the system that allows cancer cells to find alternative pathways to cope with and adapt to changes in their environment.

**3. Cancer: then and now**

Of the 52.8 million deaths globally in 2010, 8 million were from cancer (15% of all deaths). This cancer death rate was 38% more than 2 decades ago (Lozano et al., 2012). With 14 million new cases and 8.2 million deaths, cancer worldwide contributed to 15% of all deaths in 2012 (May 2014). According to the IARC's latest predictions, these figures are expected to rise to 22 million new cases and 13 million deaths annually within the next 2 decades.

More than 4 decades have passed since the National Cancer Act was signed (US Senate, 1971), but there has only been about a 10% decline in cancer deaths in the United States (Jemal et al., 2010). Even this meager progress is contested: was the decline the result of major breakthroughs and treatment or prevention? Over 1.6 million new cancer cases and 600,000 cancer deaths are projected to occur in the United States in 2014. Today, 1 in 4 deaths in the United States is due to cancer (Siegel et al., 2014).

The toll of cancer in the world not only causes human catastrophe but also inflicts a heavy social and economic burden. It strains national healthcare systems, especially in those countries with an aging population. Cancer poses a significant threat to national economies and to the global economic system, as the world has spent several hundred billions of dollars on research in the quest for a cure for cancer in the last 4 decades (Eckhouse et al., 2008). This is why the World Economic Forum lists cancer as the noncommunicable disease with the most likely and most severe risks to the global economy (World Economic Forum, 2011).

The number of scientific papers, books, projects, and patents with the term "cancer" in the title most probably

far exceeds any other topic in all the sciences. The number of scientific articles with the word "cancer" have almost tripled every decade (Figures 1 and 2), with the top 20 publishing countries having the biggest share (Figures 3 and 4). A decade ago, the total number of cancer genes accounted for about 1% of the human genome. Now this figure is 2%. Major international projects, such as the Cancer Genome Atlas and the International Cancer Genome Consortium, are underway, aiming to create a comprehensive catalog of all the genes responsible for the initiation and progression of cancer.

With rare exception, once a cancer metastases the likelihood of surviving the cancer today is about what it was 40 years ago. What is more, the obesity problem and the sedentary lifestyle in today's society are expected to increase the morbidity and mortality rate of cancer in the coming decades and will further inflict a crushing burden of economic costs and human suffering. Except for a few cancers (e.g., testicular cancer, some childhood leukemias, and lymphomas), we still have no cure for cancers once the disease is metastasized. The death rates of some cancers are rising, especially those associated with obesity and a lack of exercise, such as colon, kidney, pancreas, and liver cancers. Considering the plethora of new findings compared with a decade or so ago, the cancer puzzle today is more troubling than ever. One thing is for sure: the more we know about cancer, the less we understand it. Every answer in cancer research brings more questions.

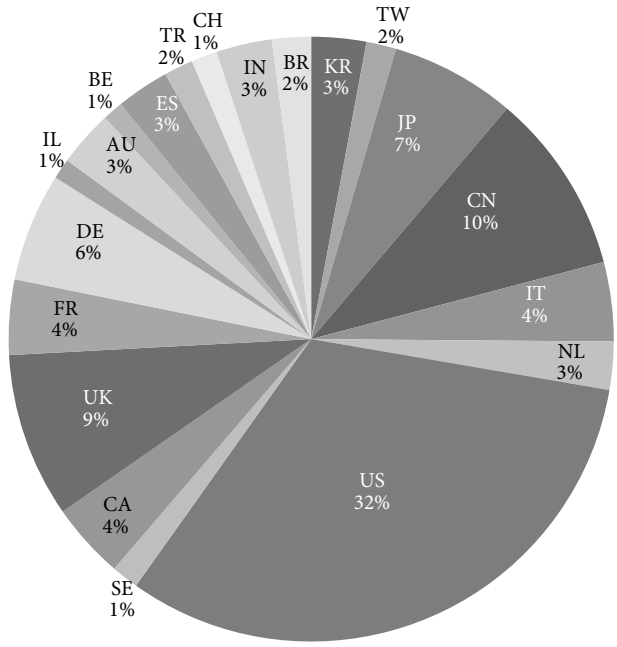



**Figure 3.** Top 20 countries in cancer publications based on number of articles with "cancer" in the title between 2008 and 2012 (5-year coverage). Total number of publications in this period was 3,021,402. Percentage value for each country is the ratio of cancer articles in that country to total cancer articles across all 20 countries. Two-letter country codes are from the International Organization for Standardization. Data were compiled online (http://dan.corlan.net/medline-trend.html).

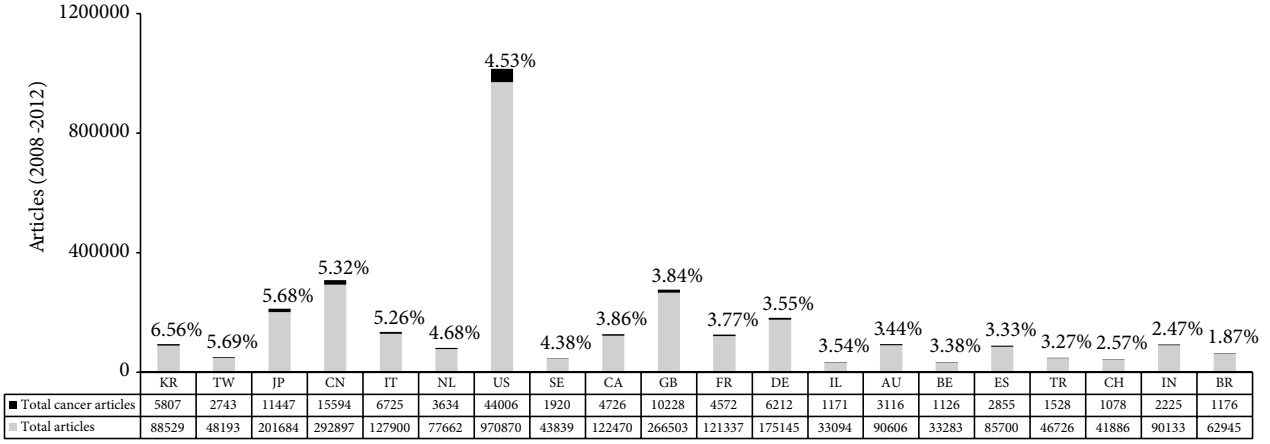
**4. Future perspectives**

Our cells do not reside in a vacuum. Except for circulating blood cells, most of our cells are anchored in their places in a specific milieu in a specific tissue. Besides inherited defects that we receive from our parents in the first place, inefficiencies in the replication of genetic material and its constant exposure to a myriad of insults during a lifetime cause mutations known or suspected (now over a million) to have roles in cancer (http://cancer.sanger.ac.uk/cancergenome/projects/cosmic/). How these various mutations hijack normal cellular processes to promote cancer still remains a mystery.

As was the case for classic biochemical and genetic studies for decades, cancer research also followed a reductionist path (e.g., investigation of single proteins or genes) to determine how cancer cells differed from normal cells. Now we know that cancer deserves a holistic approach, more so than any other human ailment, as it is caused not only by relevant genetic mutations but also by epigenetic marks (methylation in DNA and acetylation in chromosomal proteins) that also alter gene expression, metabolism, and cellular signaling. These epigenetic factors, by turning switches on and off, affect the expression of genes without causing mutations.

Epigenetic marks are the response of our genome to environmental changes. This response can have a long-term impact on the activity of our genes. If DNA is the "naked body", then one can think of epigenetic marks as the "clothing". Circumstances (e.g., lifestyle) cause the naked body to dress differently and thus behave differently. Thus, the whole genome is highly dynamic and never static. Recent studies show that overexpression and downregulation of genes through epigenetic alterations and dysregulations are deeply involved in cancer initiation and progression (Maruyama et al., 2012; Timp and Feinberg, 2013).

With the advent of massively parallel sequencing tools and technologies, now the high-resolution characterization of the whole genome, transcriptome, and epigenome of cancer cells is within our reach. However, such technologies only give us the tools to acquire data. The analysis of these data to interpret how a cancer cell initiates and progresses is the main challenge. In this context, it is striking that a complete understanding of the human oncogene (*RAS*) is still lacking, even though it was discovered 3 decades ago and is among the most studied and best characterized of the cancer-causing genes

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|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Total cancer articles | 5807 | 2743 | 11447 | 15594 | 6725 | 3634 | 44006 | 1920 | 4726 | 10228 | 4572 | 6212 | 1171 | 3116 | 1126 | 2855 | 1528 | 1078 | 2225 | 1176 |
| Total articles | 88529 | 48193 | 201684 | 292897 | 127900 | 77662 | 970870 | 43839 | 122470 | 266503 | 121337 | 175145 | 33094 | 90606 | 33283 | 85700 | 46726 | 41886 | 90133 | 62945 |

**Figure 4.** The share of the top 20 counties with the highest number of entries in PubMed between 2008 and 2012 (5-year coverage). The percentage value for each country at the top of the bars indicates the ratio of total number of articles with the term "cancer" in the title to the total number of articles. Two-letter country codes are from the International Organization for Standardization. Data were compiled online (http://dan.corlan.net/medline-trend.html).

(Malumbres and Barbacid, 2003). Although *RAS* genes are the most frequently mutated oncogenes in human cancers, with a prevalence of 1 in every 3 cases, no effective drug for the inhibition of the RAS oncoprotein has yet reached the clinic (Baker and Der, 2013). This is also the case with many other well-known oncogenes (e.g., *MYC*).

A complete understanding of cancer is still limited by many complexities and constraints. While each tumor is substantially different from others, in most cases even cells in a single tumor are slightly different from one another in terms of their mutated genetic makeup, aberrant metabolism, and other cellular pathways. Thus, a single model of such disarrays would not suffice, given the heterogeneity of tumors and even cells within a single tumor. Pinpointing a potent long-term therapeutic approach for many thousands of such targets (discrepancy) in a tumor is a hard task, let alone addressing these cells' fast-changing responses to treatment.

Indeed, it is now well accepted that virtually all cancers result from the accumulated mutations in genes that increase the fitness of a tumor cell over that of the cells surrounding it (Axelrod et al., 2006; Huang, 2013). When acquired mutations increase the fitness of a cell, that cell will generate more daughter cells than its neighboring cells. The result is the clonal expansion of mutant cells, a signature of natural selection (Greaves and Maley, 2012). Studies show that a genetically programmed cellular rewiring in cancer cells causes metabolic outliers that satisfy these cells' demands for growth and proliferation. The evolution of massive alterations in cancer cells gives these cells an edge in the competition to win out over normal cells. Given their continuous proliferation, cancer cells are programmed to synthesize the building blocks (amino acids, nucleotides) necessary to support biomass production rather than energy generation. Even in the presence of sufficient oxygen, cancer cells preferably carry out a type of metabolism that is indeed reserved for rapid energy demand (Cantor and Sabatini, 2012). As mentioned above, cancer cell genomes are riddled with mutations that may impair the function of a number of genes taking part in aerobic metabolism compared to a small number of genes involved in anaerobic metabolism. Although crucial for an understanding of cancer biology, these metabolic perturbations are challenging to quantify, given the dauntingly large number of reactions and metabolites in a typical cell (DeBerardinis and Thompson, 2012).

All these points are evidence that cancer will remain the most challenging of all human struggles. Given their millions of years of evolutionary acumen, cancer cells defend themselves in remarkable ways. Thus, a "silver bullet" for all cancers seems to be an unrealistic dream.

However, some characteristics unique to almost all cancers can be explored and exploited as potential therapeutic targets. Compared with normal cells, cancer cells have a highly auxotrophic character due to their highly mutated phenotype (e.g., defects in enzymes). Thus, for their survival and perpetuation, cancer cells are more dependent on external sources for many nutrients (e.g., the amino acids methionine and asparagine) for which they do not have a functional pathway of synthesis. This requirement is supplied either by normal cells or through diet. Thus, the rapid and complete depletion of the circulating pool of such nutrients impairs protein synthesis and leads to a delayed inhibition in DNA and RNA synthesis. Such impairment of cellular function renders cancer cells sensitive to death signals (Muller and Boos, 1998; Lu et al., 2003; Geckil et al., 2004; Delage et al., 2010; Agrawal et al., 2012).

Another track to explore for cancer diagnosis and treatment takes into consideration not only these cells' physiology but also their physics (Wirtz et al., 2011; Zhang and Austin, 2012; Jain, 2014; Moore and Nagahara, 2014). To date, research has overwhelmingly been directed towards the biochemistry and genetics of cancer cells. Now, however, we know that cancer cells bear distinct biomechanical characteristics (e.g., entropy, rheology, force, adhesion). These characteristics contribute to the plasticity in the detachment, migration, habituation, growth, proliferation, and invasion of cancer cells. If life feeds on negative entropy as stated by the physicist Erwin Schrödinger (von Stockar and Liu, 1999), cancer cells feed on positive entropy given their more chaotic molecular crowding. Indeed, most cancer cells are auxotrophic in metabolism. On the contrary, the higher organization (low entropy) of normal cells is maintained and sustained through long tracks of perfectly functioning metabolic and signaling pathways at high-energy demand. In a normal healthy cell, information flow is highly specified (low entropy), whereas in a cancer cell it is fragmented and defective (high entropy), which gives the cell the plasticity to switch to different signaling pathways and cellular metabolic activities under strained conditions. Quantitative theories that relate these physical spatiotemporal interactions of metastatic cells to the new microenvironment can provide us with a better understanding of the disease and more effective treatment strategies.

Although our inborn genetic make-up plays a pivotal role in our fate, it is estimated that between one-third and one-half of cancer deaths could be avoided with prevention, early detection, and treatment (Stewart and Wild, 2014). The estimate shows that the world could have saved between $100 and $200 billion in 2010 by investing in the prevention, early detection, and effective treatment of cancer. Obesity and sedentary lifestyle in today's societies seem to be the biggest obstacles to achieving this goal.

Finally, once they are no longer concerned with funds or the entangled interests of industry, or strained by continuous reporting and appraisals, cancer researchers and institutions will have better success in finding new avenues for cancer diagnosis and treatment.

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