Chapter 1

Introductory Chapter: Having a Brain is Not Necessary to Get Cancer… but Indispensable to Fight It

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Additional information is available at the end of the chapter

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1. Introduction

Approximately one in eight deaths is caused by cancer, in fact one of more than 200 types of cancer, which is equal to the number of deaths caused by air pollution and exceeds the number of deaths being a result of two oldest known and two most common diseases ever, malaria and tuberculosis, combined.

According to the Globocan statistics in 2012, liver (19%), stomach (8.8%), colorectum (8.5%), breast (6.4%), esophagus (4.9%), pancreas (4%), prostate (3.7%), and cervix uteri (3.2%) cancers claimed a majority of victims. Almost 80% of cancer cases are diagnosed in people over 55 years old. The overall number of cancer incidences is almost 25% higher in men than in women. In 2012, there were 14.1 mln of new cancer cases, 8.2 mln cancer deaths, and 32.6 mln people were living with diagnosed cancer. On the basis of the statistics of the age-standardized rates of the incidents of all non-melanoma cancers, in 2012, almost 48% cases were detected in Asia, 24% in Europe, 13% in North America, 7.8% in Latin America and the Caribbean Islands, 6% in Africa, and 1.1 % in Oceania (**Figure 1**). The highest numbers of new cancers have been reported mainly in highly developed countries like Denmark, Australia, Belgium, Norway, United States of America, Ireland, Republic of Korea, the Netherlands, and France. As many as 43% of all cases of melanoma (cancer closely related to the exposition to excessive UV radiation) are detected in Europe, 32% in North America, 9.4% in Asia, 6.5% in Oceania, 5.9% in Latin America and the Caribbean Islands, and 2.9% in Africa. Most of them are confirmed in New Zealand, Australia, Switzerland, the Netherlands, Denmark, Norway, Sweden, Slovenia, the United Kingdom, and the United States of America. A surprisingly high risk of the melanoma cancers in the Northern part of Europe is believed to be closely related to frequent foreign travels by light-skin people to the sunny south.

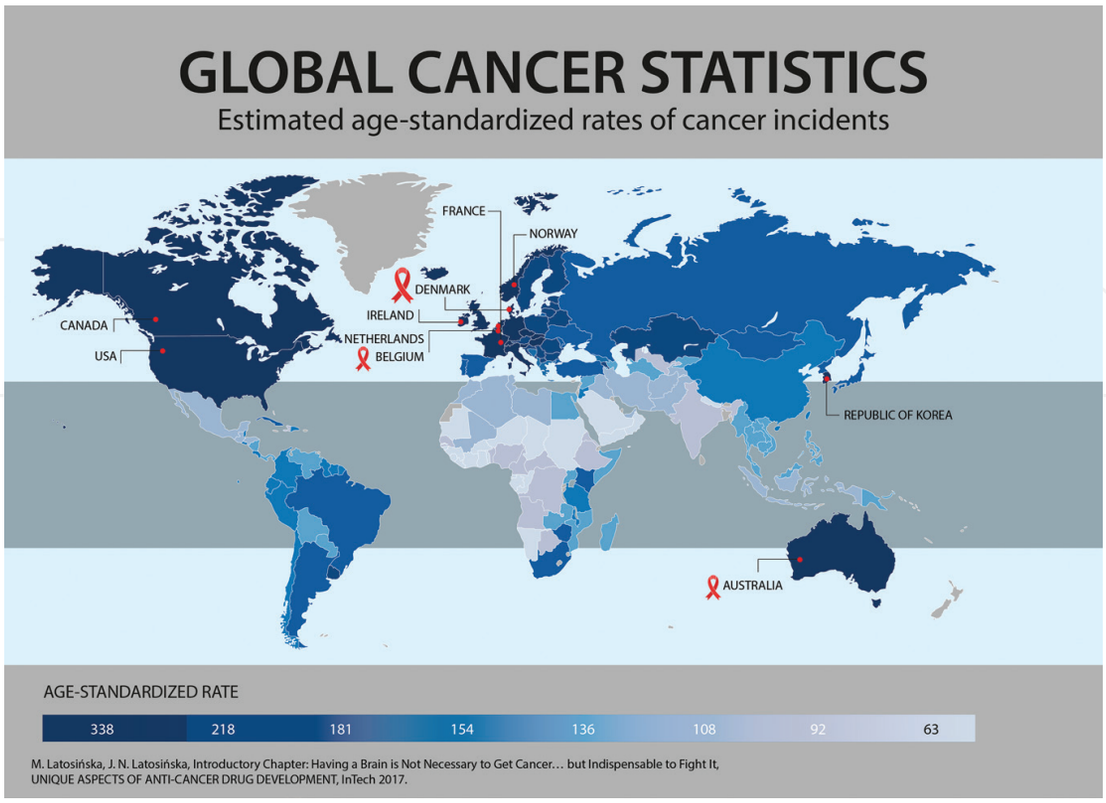

Figure 1. Non-melanoma cancer cases around the world in 2012 (statistical data: Globocan).

2. Cancer is as old as multi-cellular life on the Earth

It was long believed that cancers, especially malignant ones, are the domain of our time, because cancer cases have been scarce in archaeological excavations. But in fact, cancer has been known forever and has not necessarily been related to civilization or geographical location and definitely not limited to humans [1]. It may well appear in animals as well as in plants.

The oldest evidence of cancer dates back to about 60–70 million years ago and has been found in fossilized remains of a dinosaur in Wyoming. In the human fossils [2, 3], to this day, only about 200 cancer cases have been found, which probably count for only a small fraction of all cancers. Most of them are bone tumors either originating in skeletal tissue or being a result of metastasis. According to contemporary statistics, about 90% of neoplasm cases are carcinoma, which is formed from the epithelial tissues inside the organs or body cavities, that is, soft tissue. The natural body decay limits the possibilities of finding cancer cells to the remaining 10% in the skeletons or mummies. Although primary bone cancers are very rare, metastatic ones are very common and allow detection of traces left by primary cancer. Until 2016, the oldest specimen of cancer has been considered the hominid malignant tumor (probably Burkitt's lymphoma) found in 1932, in Kenya, in the remains of a body (mandible) of either *Homo erectus* or an *Australopithecus*. In 2016, a much older, 1.7-million-year old, hominin primary malignant cancer osteosarcoma from Swartkrans Cave, South Africa [4], and a benign bone tumor osteoid osteoma in the hominin

Australopithecus sediba from Malapa, South Africa, dated to 1.98 million years ago [5] were discovered. Both the abovementioned bone tumors often occur in young people and are not correlated with factors related to the modern lifestyle. Newer evidence covers three primary bone cancers—osteosarcomas—dated to Neolithic (Bassa Padana, Italy) [6], 1500–1070 BC (Egypt) [6], and 800–900 BC (Münsingen, Switzerland) [7]. Secondary bone cancers are much more frequent. The oldest evidence of one of the most aggressive cancers (primary cancer of the prostate gland) has been found in the form of osteoblastic proliferation in the skeleton of a mature male in Neolithic mass burial (ca. 5000 years BC). In 2015, a 4200-year-old skeleton of an Egyptian woman, whose breast cancer spread to her bones (metastatic cancer), was found in a tomb in the Nile Valley, Sudan. Osteoblastic and osteoclastic lesions, being an evidence of metastasis, have been found in the skeleton of a 40–50-year-old Scythian king, who lived 1700 BC in Southern Siberia (Russia) [8]. Excavations in Amara West, Sudan, revealed the spread of primary cancer to the collar bones, shoulder blades, upper arms, vertebrae, ribs, pelvis, and thigh bones on the skeleton of a 25–35-year-old male dated to around 1200 BC [9]. Apart from the abovementioned cases, multiple myeloma dated to 4000 BC (Mauer, Austria), nasopharyngeal, 3000 BC (Giza, Egypt), and 2300–1800 BC (Naga-ed-Deir, Egypt), metastatic carcinomas, 2200–800 BC (Czech Republic) and 1500 BC (Russia), tumor in pelvic bone in mummy, 2000 BC (Alexandria, Egypt) have been discovered. Newer evidences of fossils with metastasis are dated to the first century AD, Italy [10], Hungary [11], medieval times Switzerland [12], Hungary [13], Denmark [14], England [15–17], and Persia and Peruvian Incas in pre-Columbian America (around 1400 AD) [18]. Clearly, the majority of evidence comes from Europe and Egypt, which results from extensive excavation works and excellent preservation of mummified and skeletal human remains, but individual cases originated from Australia, North and South America are also known.

The evidence of cancers comes not only from fossils but also from written records dating back to ancient times (3000–1500 BC, Mesopotamia and Egypt). The symptoms, differentiation between benign and malignant neoplasm, and the surgical methods of treatment have been described in Egyptian Papyruses including the Edwin Smyth (2500 BC), Leyde (1500 BC), and George Ebers (1550 BC). The first description of cancer *per se*, in fact breast cancer, and information about the lack of treatment, comes from the Smyth papyrus (the so-called case 45), which nowadays is assumed to originate from Imhotep, a great Egyptian physician who lived around 2625 BC (Old Kingdom). The Code of Hammurabi, Babylonian law code of ancient Mesopotamia dated to 1750 BC, set up the standard fee for surgical tumors removal. The Rites of the Zhou Dynasty, a collection of social forms, governmental system, and ceremonial rites, written from 1046 to 256 BC, mentioned the treatment of the cancer stages (swellings and ulceration, necrosis, and ulceration). The first medicine, in the form of arsenic paste, is mentioned in the Hindu epic poem, the Ramayana, dating back to 500 BC. Different benign and malignant types of tumors were described in the fifth century BC by Hippocrates of Kos famous Geek physician. He has found blood vessels around a tumor resembling a crab in its shell and introduced the name of this disease *karkinos* (crab in Greek). The same associations had Marco Polo, who in the *Travels of Marco Polo*, a thirteenth century travelogue, described a female reproductive organs disease called "the crab" (a woman died after rupturing it in her abdomen). Hippocrates also formulated the humoral theory of cancer genesis. The story of the first successful excise of breast cancer of Atossa, the queen of Persi,

performed by Democedes, Greek Slave, is described in *Histories*, written around 440 BC by the Greek historian Herodotus from Halicarnassus. The Chinese *Huangdi Neijing* (*the Inner Cannon of the Yellow Emperor*), the oldest known medical book, dated to (475–221 BC) and (206 BC–220 AD) contained the first description of tumors including their progression, metastasis, and death but also therapies: spiritual, pharmacological, diet, acupuncture, and treatment of respiratory diseases. Nearly 400 years after Hippocrates, Cornelius Celsus described the first surgeries on cancers and introduced the well-known Latin term *cancer*, which is used to describe malignant tumors and became the root of terms *carcinogen* and *carcinoma*. Claudius Galen, the most famous Roman Empire physician in the second century, accepted Hippocrates' ideas, but left a comprehensive description of many neoplasms and introduced a special term *oncos* (Greek). Nowadays, this term is a part of the name *oncology*—the branch of medicine that deals with cancer. Galen believed that cancer was incurable; however, some tumors were removed surgically. Between the fifth and fifteenth century, European medicals used surgery and cautery on smaller tumors and caustic pastes, usually containing arsenic, on large cancers. Apart from this phlebotomy, diet and herbal medicines were applied. During the Islamic Golden Age (eighth to thirteenth century), many of the famous Arab physicians studied classic Greek medical texts, mainly Hippocrates and Galen's ones. Rhazes and Avicenna identified several cancer types, including eye, nasal, tongue, stomach, liver, the urinary system, kidney, testis, and breast, and spleen and nerve tumor. Rhazes, in 925, and Avicenna, in 1037, described cancers as extremely difficult to treat, but curable in the earliest stages of development. Avicenna discussed the combined effect of diet and medicines on cancer progression. The properties of the herbal drug "Hindiba" (*Cichorium intybus* (L.)) used by him in cancer treatment have been confirmed about 900 years later. Albucasis (Alzahrawi), a Muslim surgeon, conducted the first breast cancer surgeries using 200 different instruments invented by himself. He described his surgical equipment in *At-Tasrif*, which quickly became a standard reference, also in Europe. In 1131, Ibn Zuhr provided the first accurate description of esophageal and stomach cancers based on autopsies. In the thirteenth century, Europe autopsies were not popular, but sometimes performed to check the internal cancers growth. However, some mysterious death has been waiting for explanation till date, for example, the fifteenth century king Ferrante I of Aragon. Autopsy of his mummy revealed a case of adenocarcinoma in the muscles of his small pelvis [19]. Some protocols of autopsy have been developed by Antonio Benivieni, Florentine physician, who pioneered their use to understand the cause of death. *De Abditis Morborum Causis (The Hidden Causes of Disease)* written by him in 1507 contains the first "printed" case report of cancer. However, the major medicinal text on cancers was that of Galen, which influenced cancer treatment until the seventeenth century and *De Humani Corporis Fabrica* written in 1543 by Andreas Vesalius. In the seventeenth century, the Dutch surgeon, Adrian Helvetius, performed lumpectomy and mastectomy to cure breast cancer. The Italian, Bernardino Ramazzini, the founder of occupational medicine, was the first who linked lifestyle with the development of cancer. He described the health hazards of chemicals, dust, metals, repetitive or violent motions, odd postures, and other disease-causative agents encountered by workers in the 50 most important occupations in *De Morbis Artificum Diatrib* (*Diseases of Workers*) published in 1700. In 1761, the Englishmen John Hill published the first paper linking tobacco and cancer; 14 years later Percival Pott identified the first occupational carcinogen—soot. By the end of the eighteenth century, hundreds

of materials were recognized as carcinogens. In 1845, Virchow identified and published a description of the blood cancer disease and proposed the name leukämie (eng. *leukemia*); properly diagnosed rare chordoma tumor originated from the clivus, and later in 1888, during postmortem examination of Kaiser Frederick III body, he identified the epidermal cancer of larynx (hybrid verrucous carcinoma). Virchow also linked the cancers (e.g., mesothelioma, lung, prostate, bladder, pancreatic, cervical, esophageal, melanoma, head, and neck) with long-term inflammation [20], which was earlier suggested by the Dutch, Hermann Boerhaave. In 1842, Domenico Antonio Rigoni-Stern after the statistical analysis of cancer incidence and mortality in 1760–1839 in Verona concluded that cancer death rate is rising, increases with age, is less frequent in the country and is more likely among unmarried people.

In the past centuries, till half of the eighteenth century, the life spans hovered around 30 or 40 years, that is, was much shorter than 55 achieved in Europe only in 1920. People did not live long enough to get cancer, were killed during wars, murdered, poisoned, or were suffering from diseases other than cancer, for example, schistosomiasis, malaria, hookworms, cholera, plague, or tuberculosis. Cancer-related mortality grew by about 30% from 1900 to 1916, also due to the mass introduction of Roentgen's discovery, X-ray, to medicine and industry, which applied without any limitations and knowledge of doses resulted in cancers. Many scientists and doctors working with X-ray radiation suffered from radiation-induced cancers, including Roentgen, who died of intestinal cancer [1, 21]. But since 1926, cancer has become the second most common cause of death, just behind the heart disease.

Currently, cancer is considered as the second after heart disease as the most frequent natural cause of death among world leaders. Hatshepsut (1507–1458 BC), the fifth pharaoh of the eighteenth Dynasty of Egypt, died of bone cancer. Galerius (Roman Emperor, 305–311) likely died of bowel cancer. Napoleon Bonaparte (1769–1821) died from stomach cancer, which earlier killed his father Carlo. Among UK rulers, Edward I, Hammer of the Scotts (1239–1307) and Henry V (1387–1422) probably died of cancer of the rectum, Kenneth I (810–858) of neoplasm, Mary I (1516–1558) of ovarian cancer, George VI (1895–1952) of lung cancer, and Edward VIII (1894–1972) of throat cancer. The Queen Mother (1936–2002) battled the colon and breast cancers. Three among 266 popes died due to cancer: pope Clement VI (1291–1352) of tumor, Pius V (1504–1572) believed to have died due to undefined cancer, and Saint John XXIII (1881–1963) of stomach cancer. Saint John Paul II (1920–2005) has benign intestinal tumor removed in 1992. Henry Pu Yi (1906–1967), the last emperor of China before the Xinhai Revolution, died of kidney cancer, while the father of modern China Sun Yat-sen (1866–1925) died of liver cancer. While many USA presidents, vice presidents, and first ladies have been plagued with cancer, the only one USA president who has passed away due to cancer (throat cancer) was Ulysses S. Grant (1822–1885), a heavy smoker, while American first ladies Pat Nixon (1912–1993) died of lung cancer and Jacquelin Kennedy Onassis (1929–1994) died of lymphoma. Other presidents who died of cancers include Francois Mitterrand (1916–1996), the president of France, of prostate cancer, German president Paul von Hindenburg (1847–1934) of lung cancer, while Willy Brandt (1913–1992), the Chancellor of West Germany, of colon cancer, José Napoleón Duarte (1925–1990), the Junta leader and president of El Salvator, of stomach cancer, Corazon Aquino, the eleventh president of the Philippines, of colon cancer, and María Eva Duarte de Perón (Evita) (1919–1952), the first lady of Argentina, of uterus cancer.

Many British prime ministers died of cancer: Arthur Chamberlain (1869–1940) of bowel cancer, David Lloyd George (1863–1945) of prostate cancer, Anthony Eden (1897–1977) of liver cancer, Harold Wilson (1916–1995) of colon cancer, and Andrew Bonar Law (1958–1923) of throat cancer. Those who died of cancers include three Canadian prime ministers John Abbott (1821–1893) of brain cancer, a father of Canadian medicare, Tommy Douglas (1904–1986) of inoperable cancer, and one of the best Canada's prime ministers Pierre Trudeau (1919–2000) of prostate cancer.

According to the statistics among famous people (scientists, actors, writers, poets, etc.), lung (27%), leukemia (10.5%), pancreas (10.4%), prostate (7.7%), breast (7.4%), brain (6.9%), and stomach (6.2%) claimed a majority of victims. Surprisingly, heart diseases are much less popular cause of death. Cancer collects harvest among the most brilliant scientists like French mathematician/physician Blaise Pascal (1623–1662)—stomach tumor, James Clerk Maxwell (1831–1879), Scottish mathematician, physicist—abdominal cancer, Robert Oppenheimer (1904–1967), theoretical physicist and father of the atomic bomb—throat cancer, Enrico Fermi (1901–1954), Italian/US nuclear physicist—stomach cancer, Maria Skłodowska-Curie (1867–1934), the only person to win a Nobel Prize in two different sciences physics and chemistry—leukemia, Irène Joliot-Curie (1897–1956), her daughter—leukemia, Rosalind Franklin (1920–1958), the author of X-ray photographs, which proved that the DNA molecule is a helix—ovarian cancer, Francis Crick (1916–2004), who used Franklin's brilliant discovery and win Nobel Prize—colon cancer. Ada Lovelace (1815–1852), an English mathematician considered the first computer programmer, died of uterine cancer. Among famous persons who died on cancer are scientists representing all fields of study, for example, Elinor Ostrom (1933–2012), American economist—pancreatic cancer, Eli Lilly (1839–1898), American pharmaceutical chemists, Caro Lucas (1949–2010), Iranian Armenian Engineer, Edsger W. Dijkstra (1930–2002), Dutch computer scientists, Adam Ulam (1922–2000), Polish-American historian, political scientist and writer—lung cancer, Ernest J. Briskey (1930–2006), food scientist—leukemia, Hugh Latimer Dryden (1898–1965), American aeronautical scientist, Daniel Weinreb (1959–2012), computer scientist working in the Lisp environment, Gerrit Jan van Ingen Schenau (1944–1998), physicist, Allen Newell (1927–1992), computer scientist and cognitive psychologist. Suzanne Corkin (1937–2016), a pioneer in the field of cognitive neuroscience, died of liver cancer. Quantum physicist Deborah Jin (1968–2016), who obtained the first fermionic condensate, also died on cancer. Cancer reaches businessmen Steven Jobs, Apple Inc. – pancreatic cancer, actors (Paul Newman—lung cancer, Humphrey Bogart—throat cancer, Jack Lemon—colon cancer, Farrah Fawcet—anal cancer, Judy Holliday, Yul Brynner—lung cancer, Audrey Hepburn—colorectal cancer), poets (e.g., Arthur Rimbaud—bone cancer) and musicians (Duke Ellington, Samuel Barber—lung cancer, Joe Cocker—lung cancer, Robbin Gibb—colon and liver cancer, David Bowie cancer, Bob Marley—brain and lung cancer). Cancer reaches saints as well as gangsters (Bugs Moran—lung cancer, Jamie Daniel, Mark Chopper), American mafia bosses (John Gotti), serial killers (Ian Brady, Richard Ramirez), or nazists (Klaus Barbie, Aribert Heim—intestinal cancer). The last members of the most famous families into the darkness of history were knocked down by the cancer (Anna Maria Luisa de'Medici—breast cancer).

The evidence of cancers has taken sometimes surprising forms. Only in the twentieth century a few cases of surprising Renaissance methods of cancer documentation were discovered. The famous Michelangelo's marble statue "*Night*", located in the Medici tomb (Medici Chapel, Church

of San Lorenzo, Florence, Italy) and dated to 1520–1534, presents a female figure with owl—the night bird, symbol of feminine energies, the moon, magic and darkness, prophecy and wisdom. The left breast of this statue is completely different than right, and has abnormalities associated by oncologist with locally advanced cancer [22]. Another "clinical documentation" of the cancer stage contains "*La Fornarina*" by Rafael Santi painted in 1520. The left breast of "*La Fornarina*" is enlarged and deformed due to cancer; it is even possible to describe the stage of the breast cancer [23]. Niccolò Renieri Vanitas "*Allegory of Transience*", Keresztény Múzeum, Esztergom, Hungaryl, from 1626, also show cancer in advanced stage. A similar case of multifocal breast cancer was found in Lucas Vorsterman of a Ruben's painting after Titian's which shows a young woman dressed in a fur coat and a hat. Two lumps in the upper external quadrant of her right breast indicate a deep tumor [24]. Three Rubens paintings "*The three Graces*" ca. 1630–1635, "*Diana and her nymphs pursued by satyrs*", ca. 1636 and "*Orpheus and Euridice*", ca. 1636–1637, Prado Museum, Madrid, Spain, also indicate breast cancers [25]. In the "*The three Graces*" painting the tumor, between the left breast and the left axial, is exophytic, irregular, with inflammatory, while in two remaining show abnormalities suggesting the early stages of the breast cancer. Another example is Il Cerano painting "*The Madonna Delivers Milan from the Plague*" from 1631, located in the church of Santa Maria della Grazia, Milan, Italy, which depicts a young woman with ulcerating right breast cancer [26]. In 1654, Rembrandt Harmenszoon van Rijn painted his mistress Hendrickje Stoffels, later died after a long illness, as "*Bathsheba at her bath*". In 1967, the asymmetry and blue mark on her breast has been interpreted by Australian surgeons as a case of breast cancer [27]. The controversy whether Rembrandt indeed depicted cancer remains unsolved until today. Knowing that breast cancer has been responsible for the deaths of about 25 million women throughout history, it seems not surprising that this form of cancer was indeed documented by the artists. Nonetheless, old masters with photographic realism of painting introduced by Leonardo da Vinci can be considered as clinical photographers of their age.

Cancer is a common disease in the whole animal kingdom, with the average annual rate of all cancer types in dogs [28, 29], cats [29], horses, rates, mice [30, 31], or cattle close to that noted in humans. The cancer cases among the domestic animals are better documented than in wild ones, and suggest similar types of cancers developing in them and in humans [32]. Even aquarium fish develop bumps or lumps, internal tumors and cancers, much like humans and other animals. For example, Koi fish are susceptible to the reproductive organs tumors, goldfish to fibroma tumors and sarcomas, while gypsy-swordtail fish develop malignant melanoma skin cancers. The studies of cancers in wild populations deliver more interesting, unique data on the methods of the cancer spread as well as its origins. For example, the studies of Tasmanian devils reveal that Devil facial tumor disease, able to kill almost 90% of their population, has been spread as infectious tumors [33] similar to canine transmissible venereal tumor. This cancer cell line most probably appeared 200–2500 years ago in wolf, coyote, Siberian Husky, or Shihtzu dogs. The studies of sea animals like sea lions, which suffer from urogenital cancers [34], and beluga vales, which predominantly die due to intestinal cancer [35], indicated the role of organic pollutants in carcinogenesis. Also widely performed sharks studies revealed a lot of kidney [36] or melanoma [37] cancer cases, which put down the misleading conviction that sharks are cancer-free and that shark cartilage can cure cancer. However, a few species of animals, which seem cancer resistant and get cancer very rarely, have actually been discovered. It is known that taller people/larger dogs are slightly more cancer-prone than shorter people/smaller dogs. But surprisingly, this rule is not applicable

to elephants or whales. Elephants, which have trillion more cells than humans and reach 56 years in the wild, have much lower cancer rates than humans. Thus, evidently cancer prevalence is not correlated with body size, which is called "Peto's paradox." It has been discovered that elephant's genome is unique and contains 20 copies of a tumor-suppressor p53 (cancer-fighting gene playing the most important role in protecting against cancer) in contrast to other mammals, which have only one. A mutation of p53, which switches off this gene, found in 50% human cancers, allows abnormal cells to proliferate and form tumor. Bowhead whale species of family *Balaenidae* Gray, 1821 with over 1000 times more cells than humans, the longest-living animals that can live over 200 years, also have low cancer incidence as compared to humans. It has been found that they possess special adaptive genetic changes—genes involved in DNA repair, cell-cycle regulation, cancer, and aging. The naked mole rat (*Heterocephalus glaber* Rüppell, 1842), which is not naked, is not a mole, is a rodent but not a rat and lives up to 30 years, has been announced unique cancer-free species and a proclaimed animal of 2013. Extensive studies have revealed that its fibroblasts secrete extremely high-molecular-mass (five times larger than human) hyaluronan, which mediates the cancer resistance [38]. But in 2016, it has been discovered that these animals also may have cancer [39, 40]. Cancer has been diagnosed even in invertebrates like flies and worms [41] as well as very primitive animals like spoons [42], cnidarians [43] or freshwater hydra [44], which do not have a recognizable brain. In-depth studies show that hydra tumors share several features similar to human tumors. All this evidence suggests that cancer may be as old as animal organisms.

In human and animals, cancer develops as a result of deregulation of cell growth which is often triggered by mutation. Plants can also experience cancer which is called canker (necrosis of the bark and cambium on stems, branches, or twigs) and brought on via infections by fungi, bacteria, viruses, or insect infestation. Some tree species (cultivated or wild) are especially prone to canker development. For example, *Nectria cinnabarina* (Tode) Fr. genus of *Ascomycete* (Berk.) Caval.-Sm. fungi is a pathogen of tree species including apple (*Malus* (Mill.)), ash (*Aesculus* (L.)), birch (*Betula* (L.)), golden rain tree (*Koelreuteria paniculata* (Laxm.)), honey locust (*Gledetsia triacanthos* (L.)), maple (*Acer* (L.)), mulberry (*Morus* (L.)), and oak (*Quercus* (L.)); *Leucostoma* Meigen, 1803 and *Valsa* Fr. cause canker diseases in maples (*Acer* (L.) spp.), plums and peach (*Prunus* (L.) spp.), poplar and cottonwood (*Populus* (L.) spp.), willow (*Salix* (L.) spp.) elm (*Ulmus* (L.) spp.), and spruce (*Picea* (A. Dietr.) spp.); while *Phomopsis arnoldiae* (B. Sutton) is responsible for Russian olive (*Eleagnus angustifolia* (L.)) cankers. *Leucostoma persooni* (Nitschke) Höhn. and *Leucostoma cinctum* (Fr.) Höhn. are some of the most destructive pathogens on peach and ornamental plums (*Prunus* (L.) spp.). *Pseudomonas syringa pv. Syringae* Van Hall, 1904 and *Pseudomonas syringa pv. Morsprunorum* (Wormald) are responsible for the most cankers of many fruit trees like cherries (*Cerasus* (L.)), apricots (*Prunus* (L.)), and peaches (*Prunus persica* (L.) Batsch 1801). Thus, the majority of plants are unique host species for selected canker-causing organisms. However, plants are a bit less vulnerable to the cancer phenomenon and cancer effects than animals or humans. The walls of their cells are thick, thus the cells, including canker ones, are well separated. Therefore, the cancer can grow in separate parts of plant, but is unable to metastasize. Furthermore, plants lack the vital organs which after the cancer attack would quickly lead to their death. But the diffuse trunk cankers of chestnut (*Castanea dentata* (Marshall) Borkh.) caused by *Cryphonectria Murrill* Barr. parasitica or read oaks like Coast live oak (*Quercus agrifolia* (Née)), California black oak (*Q. Kelloggii* (Newb.)), and Shreve oak (*Quercus parvula var. Shrevei* (Greene)) cankers being a result of *Phytophthora ramorum* (Werres, De Cock & Man in 't Veld) and trunk and stem canker of coffee

trees incited by *Ceralostomella fimbriata* (E. et H.) Elliott are still able to kill a tree in a short time. The studies of cankers are important because they confirm a relation between fungi and cancer. In fact, mycotoxins (e.g., alfatoxin) belongs to carcinogens [1], able to cause p53 mutations. External stimuli such as fungal attack (eg. *Xanthomonas campestris pv. Viticola Nayudu* (Dye)) and UV-radiation activate the stilbene synthase genes in the grapes of *Vitis vinifera* (L.), *Morus* (L.) or *Arachis hypogaea* (L.) to produce resveratrol, which fights the fungus. In the human body resveratrol is converted by Cytochrome P450 1B1 (CYP1B1) to piceatannol an anti-cancer agent that can selectively kill cancer cells. Tutankhamun or Jagiellonian curse, responsible for many death cases after opening old tombs, turned out to be the responsibility of misbehavior of mycotoxins. Therefore, it is no wonder that some scientists, like Max Gerson or Tullio Simoncini, formulated the hypothesis that human cancer is a fungus, which form colonies and spread throughout the host area. Maybe the species from plant and animal kingdoms are attacked by the species from other kingdoms?

Anyway, the human, animal, and plant studies suggest that cancer may be extremely old, as old as multi-cellular life on the Earth.

3. Cancer is unique

The cancer uniqueness begins from the single cell, which after mutation is focused on survival and thus acquires very special features. Contrary to the healthy cells, cancer ones contain abnormal asymmetrically shaped nuclei, remain undifferentiated, and constantly divide, but also have the ability to form tumors by building layers on the top of each other (proliferation). Their altered metabolism based on glucose instead of oxygen and the ability to grow new blood vessels (angiogenesis) ensure continuous delivery of components necessary for cancer life. The implemented special "pro-survival" mechanism turns off apoptosis (programmed cell death). Cancer has not only limitless replicative potential but also invasive character with its ability to migrate and spread to other organs and tissues. It is in fact oriented toward its own survival exclusively, but not to the survival of the organism in which it develops. As cancer is characterized by the abnormal invasive growth of singe mutated cancerous cell, resourced by the life-sustaining chemical transformations guaranteeing uninhibited growth and immortality but also ability to metastasize and spread to other parts of the body, it is understood why it is so difficult to overcome.

The differences in individual genotype, random nature of DNA mutations inherited or developed, cumulating year by year in the organism and responsible for each of 200 types of biologically different cancers, make the cancer disease extremely complex in identification, diagnosis, and treatment. Identification of the behavior, spread, or damage made by cancer is difficult. The difficulty in fighting cancer lays in the fact that we have no idea by what exactly it is triggered, because of the number of possible factors associated with it. It can be the factors related to the body (inherited genes, hormonal imbalances, or immune system disorders), environmental factors (chemicals—hazard substances including drugs and food, biological oncogenes—viruses, bacteria, parasites, fungi, and in rare cases tumor cells, and physical—different forms of electromagnetic radiation), and psychological ones, for example, stress which alters the levels of hormones in the body and affects the immune system (**Figure 2**).

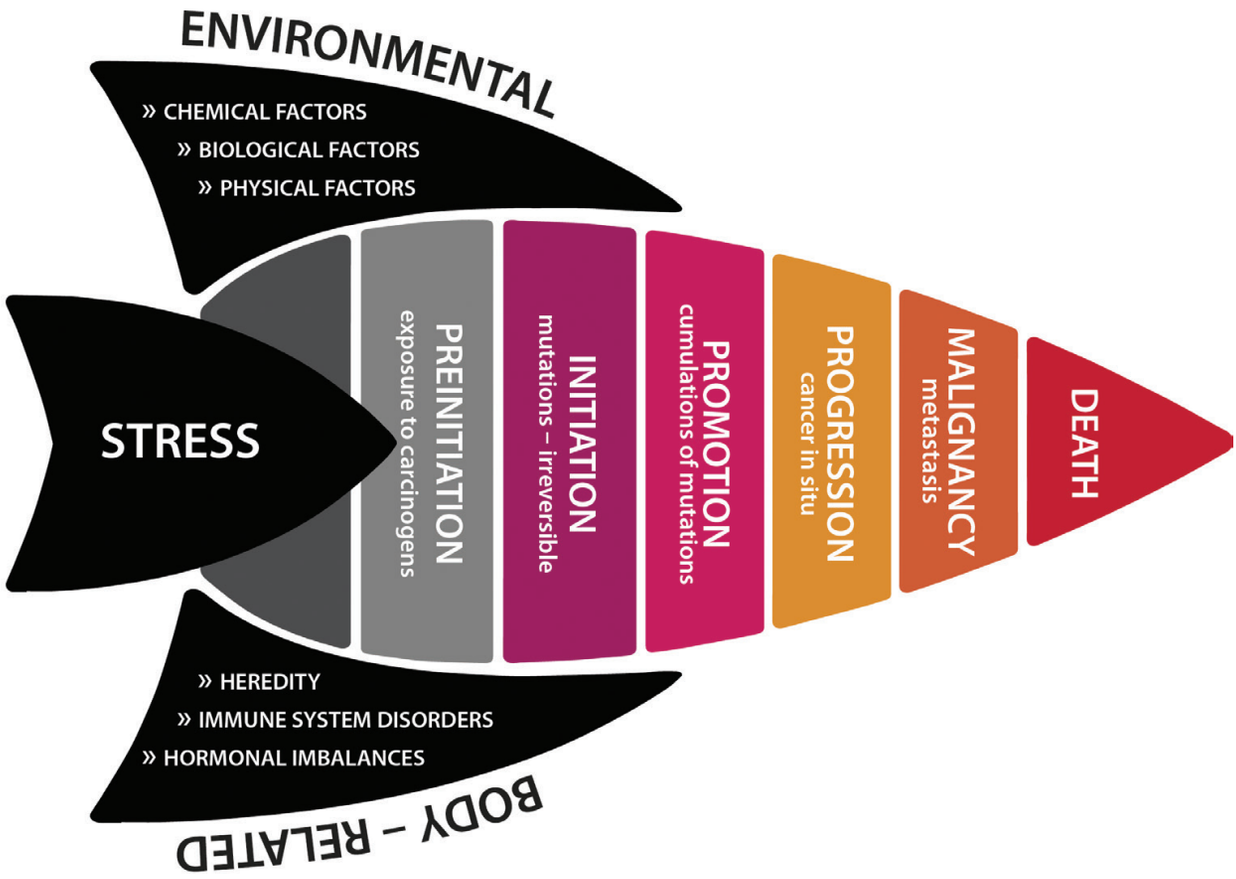

Figure 2. Multi-step process of carcinogenesis.

The problems with fast and accurate enough diagnosis at the early stage, deficit of effective anticancer drugs with no side effects as well as difficulties in access to certain parts of the body like the brain, are serious obstacles. But with insufficient knowledge, the effective treatments are hard to develop.

4. Final remarks

Matthew Neely, the Senator of West Virginia, was the first public figure who highlighted the necessity of studies on cancer. In 1928, he said that cancer is "*a monster more insatiable than the guillotine*." Shortly after the discovery that cancer had become the second most common cause of death, two large organizations in USA and Europe were established to lighten humanity's ever-growing burden of cancer. The National Cancer Institute (NCI) was established by the National Cancer Act of 1937 signed by USA president Franklin Delano Roosevelt and The International Agency for Research on Cancer (IARC), World Health Organization (WHO) agenda, was founded by the president of France, Georges Pompidou (who later died on lymphoplasmacytic lymphoma). The NCI coordinates the National Cancer Program and conducts and supports research and other activities related to the causes, prevention, diagnosis, and treatment of cancer. IARC till today published 118 volumes containing a total list of carcinogens

with 1162 entries, and provides statistics on cancer incidents and mortality around the World. In 1971, Richard Nixon, the USA president, announced "*war on cancer*" and signed the National Cancer Act Program to more effectively carry out the national effort against cancer.

Since then, cancer has been the most widely described and the most extensively studied (174 k books, 365 k journal articles, 113 k dissertations) disease. But despite significant progress in knowledge (e.g., the Cancer Genome Atlas sequencing the genomes of human cancer cells), improved-methods of diagnosis (e.g., magnetic resonance imaging (MRI), X-ray and computed tomography (CT) scans, positron emission (PET) tomography, ultrasonography, or thermography and invasive as biopsy), methods of drug discovery (studies in silico), and delivery (nanotechnology) as well as treatment (anticancer drugs combined in whole therapy lines, dietary supplements), over the last 50 years, cancer with increasing numbers of incidents and mortality still remains a major cause of death in the world and our abilities to cure it are still very limited.

Cancer is the oldest known disease, probably as old as life on the Earth. Since nearly 5000 years, it is considered as complex systemic disease, which requires combined methods of treatment (surgical—common in all periods from ancient Egypt till today, radiotherapy, and chemotherapy introduced in the nineteenth century, immunotherapy discovered recently). But because the genes contributing to cancer progression come from the organism's own cells, with the increasing lifespan the risk of cancer increases. Thus, it is naive to expect that this disease ever could be entirely eliminated. However, there is no reason to lose hope for finding an effective treatment or methods of its prevention. Recently, it has been discovered that nearly 50% of all cancers is preventable by the elimination of different factors, in particular environmental ones. Furthermore, some types of cancers or their recurrence are known to be predictable using different types of screen tests (including panel of multiple gene tests for mutations).

Being a human or having a brain is not necessary to get cancer, but really indispensable to prevent or fight it.

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