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LETTERS

Global Cancer Statistics 2022: the trends projection analysis

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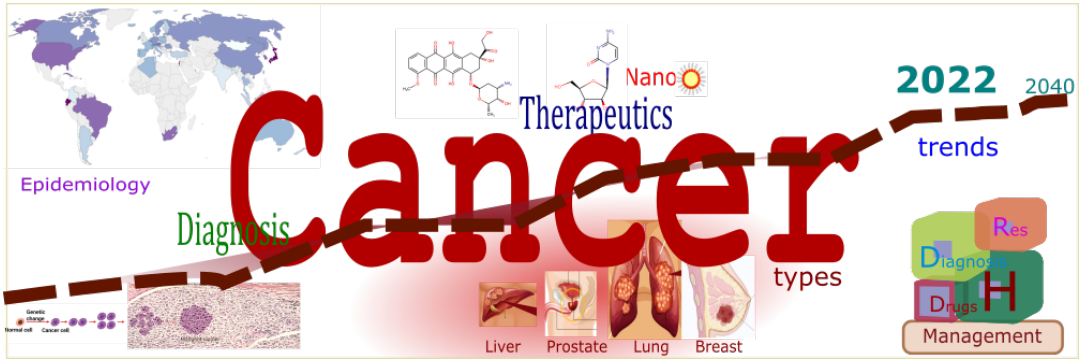
Review

ABSTRACT



Cancer is one of the most fatal diseases of recent times that causes several deaths every year. The disease variations in different parts of the world, the impact of available medical facilities, and other socio-economic factors have impacted the proper management of this disease. The comparative statistical data of cancer types like breast, prostate, colon, lung, lymph, blood, brain, and kidney cancers can be used to design treatment strategies and therapeutics development. With the advancement of science, several drugs besides diagnostic methods have emerged to control respective cancer and have assisted in curing this disease to some extent. The comparative statistics analysis for cancer about current prevalence is included here to bring a clear framework for the efforts towards future drug development to manage this disease. The availability of new diagnostics and therapeutics and advanced medical facilities in clinics impact cancer statistics. An evaluation of current trends and statistics of cancer pathology vis-à-vis theranostics (diagnostics as well as therapeutics) progress with possible application in clinical settings constitutes the core part of the discussion in this review.

Keywords: Cancer trends, Cancer statistics, Cancer types, drug status, clinical drugs, nanotherapeutics,

INTRODUCTION

Cancer, the disease of pathophysiological alterations in the inherent process of cell division,[1] has emerged as a significant disorder responsible for a large number of deaths year by year worldwide.[2] More than 19.3 million (19,300,000) new cancer cases were diagnosed and reported recently, leading to approximately 10 million deaths in 2020 based on the reported data.[3] The continuous emerging incidences of cancer worldwide that causes millions of deaths annually have generated the need and demand for developing potent pharmaceuticals for treating different cancers.[4–7]

The cancer generation is due to many factors, such as environmental influences, internal stress, or heredity.[8–10] The responsible factor varies from patient to patient and depends upon the type of cancer and geographical location.[11] The treatment needs are to be established adequately in each respective case. The change in environment (and climate) due to industrialization, along with living and food style, is considered one primary concern for increasing numbers of cancer incidences.[12] However, a proper rational link still needs to be validated to establish any valid conclusive claim.[12]

Approximately 19-20 million people are diagnosed with cancer annually worldwide.

The affected organ of origin identifies the type of cells multiplying inadvertently. Increased prevalence in the different gender or populace has been observed with the occurrence of a particular kind of cancer. For example, breast cancer is most prevalent type of cancer in women worldwide, while lung and

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prostate cancers are the primary incidences in the male population. Lung cancer is the second major cancer in males and females when counted combined.

We lose approximately 10 million people due to cancer annually. Thus, there is a need for consistent efforts to develop novel therapeutics.

The socio-economic status of a specific region is a part of environmental factors that impacts the availability of medical facilities and more effective expensive drugs. Furthermore, improper use of pesticides,[13] industrial waste disposal practices, and pollution control policies indirectly contribute to the quality of healthy living. These factors directly account for a particular region's death and disease prevalence in a specific region. The country-specific rating has been reported as shown by epidemiology (Figure 4). A glimpse reflects the relation of a disease with the socio-economic status of different parts of the world. The data reporting by different countries lags 2-4 years due to the time required for data collection, proper consolidation, and final reporting, along with varying delays in reporting death cases.

Herein, a trend analysis of the prevalence of cancer is presented based on the data recorded in different reviews and reporting sites and agencies. The review articles published recently were considered for extracting specific statistical data. The sites for international reporting agencies like the World Health Organization (WHO), International Agency for Research on Cancer (IARC), GLOBOCAN, American Cancer Society, and other countries' agencies were also used for the compilation of the statistics for this review discussion. Statistical analysis regarding the type of cancers, overall epidemiology as a relative inference from the data, and progress in therapeutics were included in the discussion. The main focus of this review is to generate an informed understanding via rational discussion from the data reported by different agencies and literature reports about the cancer incidences and deaths in the world and different regions and countries, along with the therapeutics development efforts.

EPIDEMIOLOGICAL STATISTICS

Every country in the world has been burdened with the incidence of one or more types of cancer. The Global Cancer Observatory (GCO) (gco.iarc.fr) of the IARC records the global estimates of cancer incidences and deaths. The GLOBOCAN 2020 includes the data and interactive graphical visualization of datasets about cancer incidences and deaths from 185 countries in regional and sex-based data. The tabulation and graphical visualization of the GLOBOCAN data can be accessed via the Global Cancer Observatory (GCO) (https://gco.iarc.fr).

Globally, an estimated 19.3 million incidences and 10 million deaths due to cancer were reported in GLOBOCAN 2020. Out of these total cases, the incidence of commonly diagnosed cancers worldwide were female breast (2.26 million cases, 11.7%), lung (2.21 million, 11.4%), and prostate cancers (1.41 million, 7.3%). The combined mortality due to cancer indicates the major causes of cancer death were lung (1.79 million deaths, 18% of total deaths due to cancer), liver (830,000, 8.3%), stomach (769,000, ~7.7%), and breast cancer (680,000, 6.9%) (Figure 1). In sex-disaggregated cancer incidences and deaths data, the most common cancers detected in men are lung (14.3%), prostate (14.1%), non-melanoma skin (7.2%), and stomach (7.1%) cancers, while in females the frequently diagnosed cancers are breast (24.5%), lung (8.4%), and cervix (6.5%) cancers.

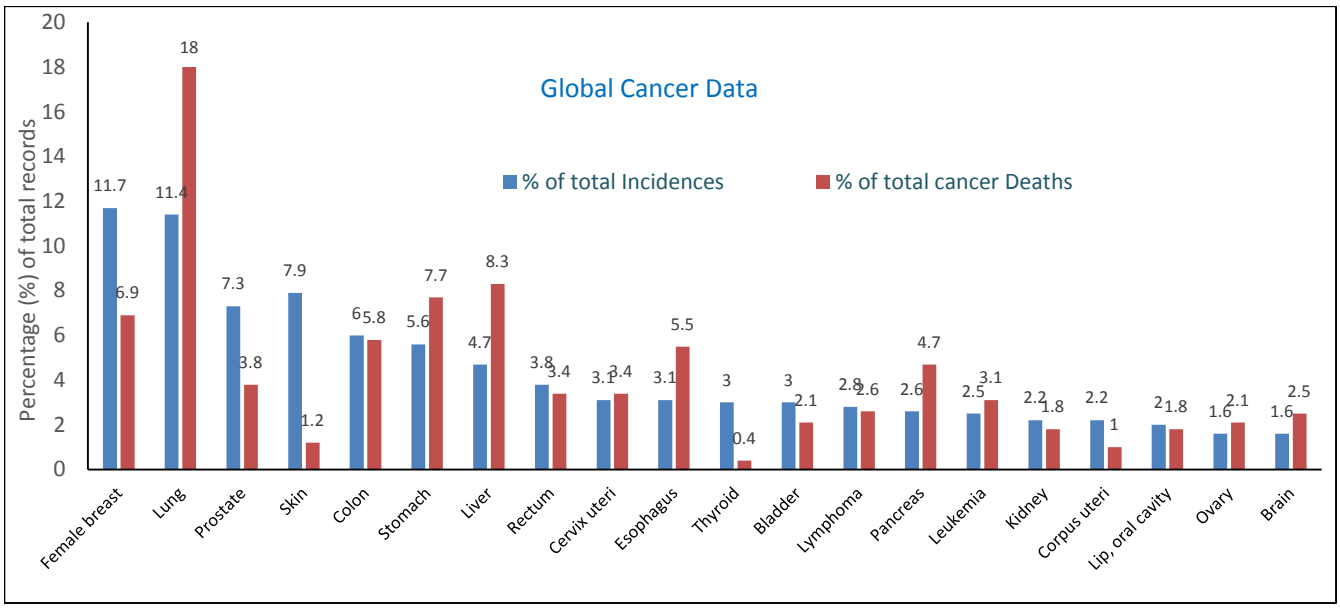

Figure 1. Relative representation in percentage of total incidences (19.3 million) and total deaths (10 million) due to cancer. Data sources: Ref [13].

Mortality-wise, the most deaths in men occurred due to lung (21.5%), liver (10.4%), stomach (9.1%), and lethality in women was due to the breast (15.5%), lung (13.7%), and cervix (7.7%) cancers (Figures 2 and 3).[3]

The GLOBOCAN data with region-wise statistics indicate that Eastern Asia reported the most cases, 6.0 million (31.1% of the total), with 3.6 million deaths (36.3%). North America reported 2.6 million cases (13.3%) with a 7% share of cancer deaths, while

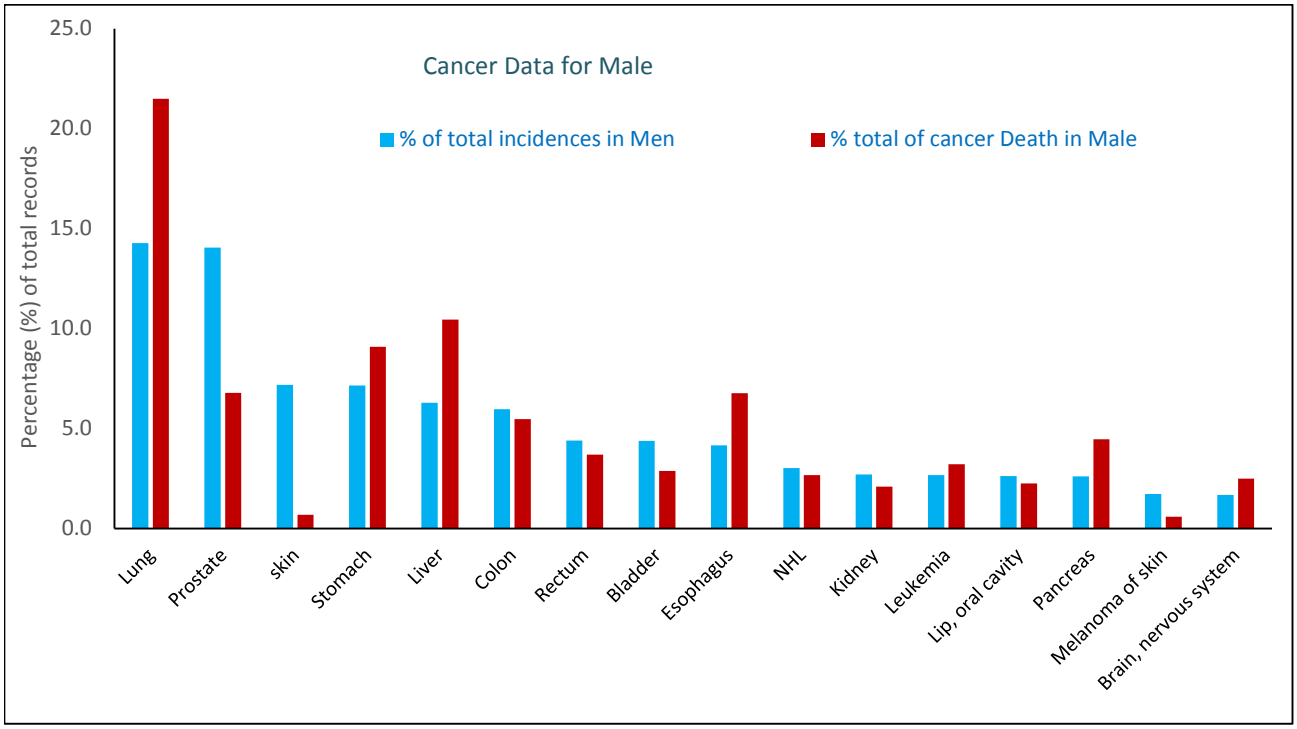

Figure 2. Relative representation in percentage of total incidences (10.1 million) in males and total male deaths (5.5 million) due to cancer for selected major cancer types. Data sources: Ref [13].

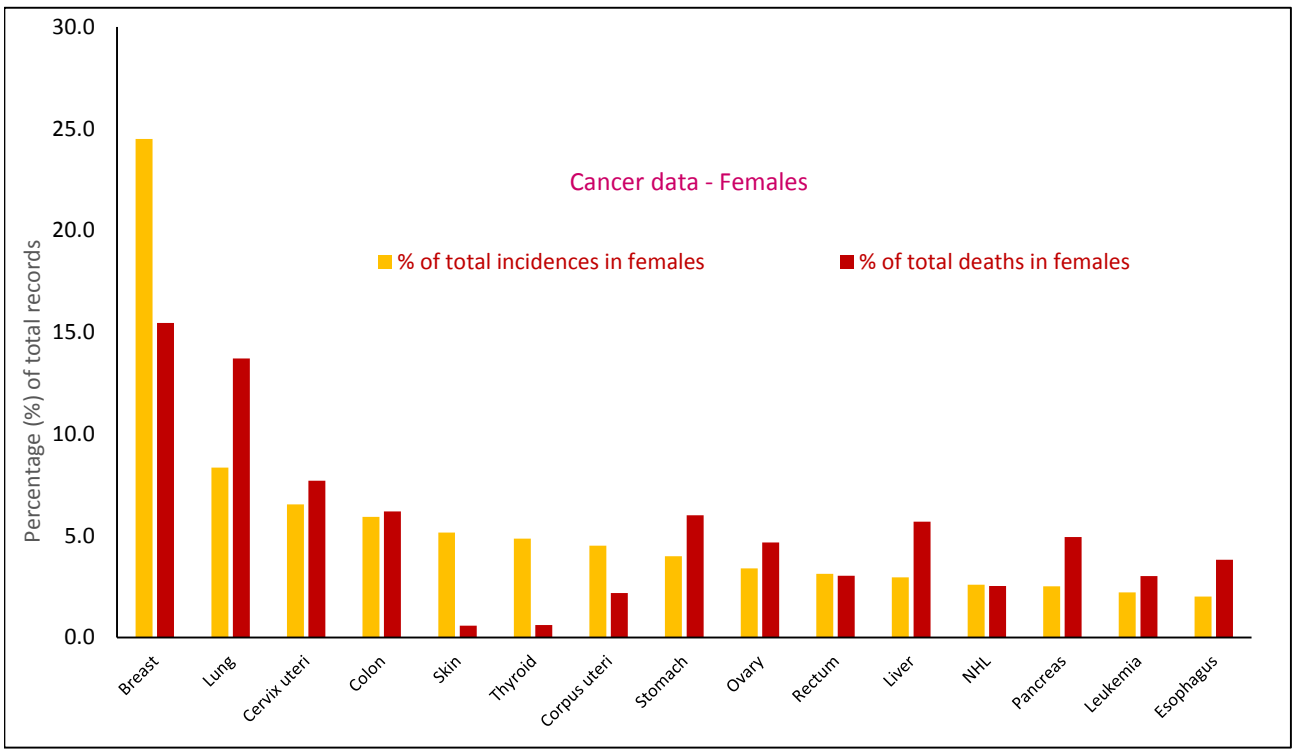

Figure 3. Relative representation in percentage of total incidences (9.2 million) in females and total female deaths (4.4 million) due to cancer for selected major cancer types. Data sources: Ref [13].

South-Central Asia recorded 1.95 million cases (10%) and 1.3 million (12.6%) deaths. Europe reported 4.4 million incidences, with 1.9 million (20%) deaths.[3] More global cancer data graphics have been reported in another review[14] and may be referred to for more details (Figure 4).[3,14] After cardiovascular diseases, cancer deaths are the second leading cause of disease-associated mortality globally (Figure 5).[15,16]

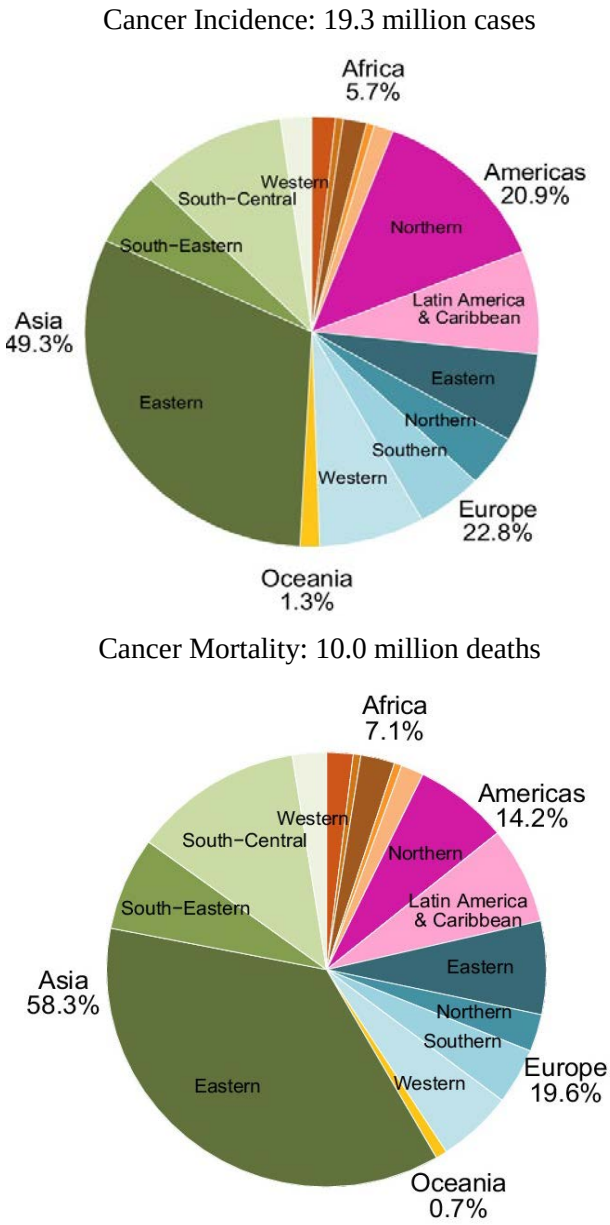

Figure 4. Region-wise percentage share of cancer incidences and deaths. Reproduced with permission from Ref [3]. Copyright John Wiley & Sons.

The GLOBOCAN estimates provide a global snapshot of the cancer burden and a graphical representation of regional or country-wide cancer incidences and mortality. The country - specific agencies report more detailed data for regional cancer incidences and deaths, and provide a point to specific regional

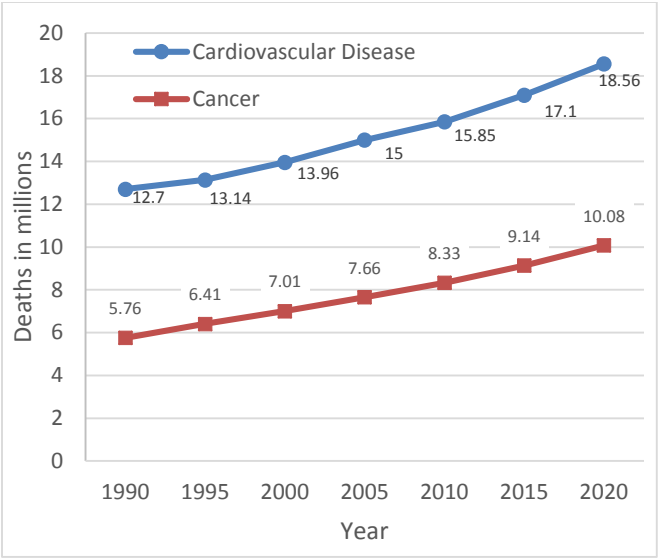

Figure 5. Relative yearly deaths due to cardiovascular diseases and cancer. Data source: Our world in Data website (ourworldindata.org).

efforts in evading or controlling plans for cancer. The country-specific count and analysis of cancer incidences and deaths provide the pondering points for thorough consideration of cancer related to the environment, social and economic standings, and hereditary influences (for relative incidences of a particular type of cancer in respective regions). Furthermore, the country-specific analysis of cancer burden highlights the need for regional and national prioritization of cancer control efforts based on the cancer patterns observed.

In the United States, the estimated total number of patients diagnosed with cancer in 2019 was 1,762,450 (1.7 million), indicating a daily diagnosis count of cancer cases of 4,800 per day.[17] Nearly 606,880 people lost their lives to cancer in the United States, according to the data for 2019, which corresponds to nearly 1,700 deaths per day.[17]

The population-based statistics have been collected by the National Program of Cancer Registries (NPCR) (of Centers for Disease Control and Prevention) since 1995 in the United States. The major incidences of cancer in the male population are the prostate (20%), lung and bronchus (13%), colon and rectum (9%), urinary bladder (7%), and melanoma of the skin (7%). In contrast, in females, breast cancer (30%), lung and bronchus (13%), colon and rectum (8%), uterine corpus (7%), and melanoma of the skin (4%) are the leading cancer types.[17]

In agreement with the global trends, breast cancer is the highest incidence in women in the United States. Breast cancer incidence rates increased by approximately 1% (average) annually from 2006-2015. This may be due to the obesity pandemic and declining parity in women.[18] Lung cancer cases have been declining continuously over the years (approximately a 3% decline in men while lung cancer incidences are getting stabilized in women).[19] The decline may be attributed to cessation in tobacco uptake variation in people. However, the conclusive link cannot be established due to variance in cases of different communities and ages.[19]

The type of cancers that cause the maximum number of deaths includes lung, prostate, breast, and colorectum in the United States. Lung cancer is the leading and stands responsible for one-fourth of all cancer deaths in the United States. In male patients, the majority of cancer deaths are due to lung and bronchus (24%), prostate (10%), colon and rectum (9%), pancreas (7%), liver (7%), while in female patients, the death toll is due to lung and bronchus (23%), breast (15%), colon and rectum (8%), pancreas (8%) cancers. In women, breast cancer incidences are leading while it is second in death tolls (15%).[17]

In 2022, 1,918,030 (1.9 million) new cancer cases and 609,360 cancer deaths are projected to occur in the United States,[20] suggesting an increase of 8.8% in cases and 0.41% in death when compared to 2019. Breast cancer continues to be the most prevalent cancer with a number of annual cases, with 287,850 incidences in 2022, while lung cancer continues to be the leading cancer for death, with approximately 350 deaths per day.[20]

The cancer data for the years 2006-2015 shows a steady trend of stable incidences of cancer in women while there is a decrease of approximately 2% incidences per year in men.[17] Lung and colorectal cancer incidences showed an accelerated decline of 3% in 2011-2015 data while prostate cancer declined to 7% incidences. Cancer death statistics for 2007-2016 indicated a decrease of 1.4% in female patients and a 1.8% decline in death in male patients. In more comprehensive data calculations from 1991-2016, there has been expectedly a 27% drop in overall cancer deaths.[17] The 2014-2018 data show a slow increase in incidences of breast cancer (~ 0.5 % increase annually), while the early diagnosis of prostate cancer remained stable. However, the advanced stage cases showed a 4 to 6% rise, making its cases to 8.2% increase compared to the past decade.[20] The advanced stage lung cancer cases declined while the primary stage (localized stage) diagnosis increased by 4.5% annually, contributing to its increased incidences compared to the past decade and the 2014-2018 duration (from 17% in 2004 to 28% in 2018).[20]

The mortality rate due to lung cancer showed an accelerated declining pattern. Similarly, the deaths due to breast cancer showed a declining pattern, while the deaths due to prostate cancer stabilized during this time. This can be attributed to developing new therapeutics over time and improving medical facilities for managing this dreaded disease. Furthermore, the improvement in early diagnosis and treatment practices has strengthened control over incidences and deaths due to breast, prostate, and lung cancer. The intervention of advanced therapeutics and targeted cancer therapy and the introduction of improved early detection and treatment have been shown to facilitate reductions in mortality due to cancer.[20]

India's cancer statistics are recorded by the National Cancer Registry Programme (NCRP) of the National Center for Disease Informatics and Research (NCDIR), Bengaluru, an institute of the Indian Council of Medical Research (ICMR). The ICMR-NCDIR-NCRP pulls the data through 36 PBCRs (Population-based cancer registry) and 236 HBCRs (Hospital-based cancer registry).[21] The approximate projected cases of cancer in India were 1,392,179 (~1.4 million) in the year 2020, leading to 850,000 (~0.85 million) deaths due to cancers.[21] The five leading cancers in India, as per reported data, were breast, lung, mouth, cervix uteri, and tongue. The sex-based incidences reported were 679,421 male patients and 712,758 female patients. Breast and cervix uteri cancers were the most common cancer types in females in India. Breast cancer incidences show steady increasing reporting trends, and the majority of incidences reported are from metropolitan cities.[22] The increasing reports of breast cancer in women pose a concern for health agencies for necessary action to control and generate necessary medical facilities.[23] Lung, mouth, esophagus, stomach, and nasopharynx cancer are prominent in males. Lung cancer, the leading type of cancer reported in metropolitan cities, is in general agreement with the trend line of global data. The presumptive association of lung cancer with tobacco smoking and prevalent air pollution in cities is consistent with this trend. The increasing use of synthetic pesticides in agriculture has also been considered a contributing factor[24] along with improper industrial waste disposal practices for increasing cancer cases, particularly associated with the prevalence of new cases of cancer in specific regions. The PCBRs data indicated the association of almost a third of cancer incidences with tobacco use (smoking and chewing) in India.[25,26] The social norms related to avoiding tobacco use have been emphasized towards preventive measures for most cancer cases in India.[21] Thus, comparing the United States and India cancer statistical data demonstrate some similarities but significant differences related to the prevalence of cancer types. In the United States, the major incidences of cancer in males are prostate and lung. However, lung, mouth, esophagus, stomach, and nasopharynx cancers are the major contributing cases in India, suggesting population-based differences.

Cancer statistics for 2022 for China have been reported recently with estimates for the projection of cancer incidences and deaths.[27] According to the report, there will be approximately 4,820,000 (4.8 million) new cancer cases and 3,210,000 (3.2 million) cancer deaths in China.[27] Cancer registry data is released by the National Cancer Center (NCC) of China to understand the cancer statistics, trends, and population profiling in China.[28] The leading cancer types incidences in 2022 will be lung (870,982 cases (18% of total incidences), colorectum (592,232 cases, 12%), stomach (509,421 cases, 10.5%), liver (431,383 cases, 9%), and breast (429,105, 8.9%) in China. The mortality trends data indicate the majority of deaths will be due to lung (23.9%), liver (12.8%), stomach (12.5%), esophagus (10.1%), and colorectum (9.6%). The major incidence of cancer in men (2,625,070 cases, 54% of total cases in China) will be of lung (21.9% of cases in males), stomach (13.4%), colorectum (13.0%), liver (12.1%), esophagus (9.0%), and prostate (4.8%). In contrast, in females (2,195,764 cases, 45.5% of total cases in China), the leading incidences of cancer will be breast (19.5% of cases in females), lung (13.5%), colorectum (11.5%), thyroid (7.7%), stomach (7.1%), liver (5.2%), and cervix uteri (5.1%). The mortality in men will be due the lung, liver, and stomach cancers, while in females, most of the death toll will be due to lung, colorectum, stomach, and breast cancers.[29] Contrary to global trends, breast cancer cases as well as mortality, will be less in women in China.[27]

Yearly trends indicate that China's stomach, liver, and esophageal cancers have decreased gradually in recent years. The overall incidence rates in Chinese women have been increasing since 2000, particularly for the most common cancer types.[27] Noticeably, the incidence rate of thyroid cancer has risen sharply since 2000 in China. The population size and aging population have been on an upwards trend in China, while compared to that, the cases of cancers have shown a stabilized pattern. Compared to the incidence rate, the fatality rate due to cancer has been in a declining mode from 2000 to 2022.[27]

In the African continent, the African Cancer Registry Network (http://www.afcrn.org/) is the central agency for corroborating and reporting cancer incidences and death statistics. The GLOBOCON 2020-based analysis reports the annual estimated 1.1 million new cases in Africa and approximately 711,429 deaths due to cancer in Africa in 2020.[30] The African countries are in a transition phase in improving the facilities for controlling the disease in different regions. The high death rate warrants a new scenario to improve cancer management medical facilities.[31] In sex-disaggregated data for African countries, the new cancer case in females accounted for 633,456 (57.5% of total cases in African countries). In comparison, the new cases reported in males are 475,753 (43% of the total).[30] The mortality for cancer in females was 387,546 (54.4% of total deaths due to cancer in African countries), while the male deaths accounted for 323,883 (45.5%). The incidence and death rates are much higher in females than males in African countries.[30] These data show a significant difference with China, where cancer incidence for males accounts for 54% of all cases.

In case of the total burden of cancer in respective African countries, Egypt was the leading country with 134,632 new cases (12.2% of total incidences in African countries), followed by Nigeria (124,815 cases, 11.3%), and South Africa (108,168 cases, 9.8%). In terms of mortality due to cancer, Egypt with 89,042 deaths (15.5% of total cancer deaths in African countries), Nigeria with 78,899 (11%), and South Africa with 56,802 (7.99%) were the top three countries in terms of cancer deaths.[30] The data indicated that breast, cervical, and prostate cancers are the three major cancers of concern. In African females, breast cancer was the leading malignancy, with 186,598 new cases (16.9% of total cases), which led to 85,787 deaths (12% of cancer deaths) in 2020. The second one was Cervix uteri, with an estimated incidence of 117,316 (10.6%) and 76,745 deaths (10.7%). Among African males, prostate cancer was the leading cancer group, with 93,173 new cases (8.47%) and 47,249 deaths (6.64%). The socio-cultural settings besides economic status have been attributed to higher incidences of cancer in African females and higher mortality, particularly for breast cancer. It has been frequently observed that the females in remote regions are hesitant to consult the medical doctor, mainly because of the existing socio-cultural norms in the society in different regions of the African countries. The efforts in African countries demand a holistic approach to controlling cancer, including vaccination drives, preventive measures, and awareness and capacity building with cost-effective diagnostics and therapeutics development.[30]

"Around one-third of deaths from cancer are due to tobacco use, high body mass index, alcohol consumption, low fruit and vegetable intake, and lack of physical activity." - WHO

STATISTICS TREND PROJECTIONS 2022

Most agencies concerned with the cancer-related data reported analysis for the year 2020, at the time of the start of the COVID-19 pandemic. The emergence of the COVID-19 pandemic in early 2020 (from the first incidences in December 2019) has placed the world in a new order of lockdown nearly up to the end of 2021.[32] The medical facilities and research units directed their resources towards the search for suitable and emergency medicine for COVID-19 treatment.[33–35] The medical staff got involved in controlling the infection. Furthermore, researchers potentiated efforts in developing viral medicines,[36–38] medical masks, sensors for detection,[39] diagnostic kits,[40] materials for surface neutralization from virus,[41] and biologists oriented their efforts towards vaccine development.[33] In all these times, the other diseases received less attention, if not wholly ignored; hence, data reporting for cancer probably became a delayed objective of agencies. Keeping with the earlier trends reported in previous years, if projected for 2022, the data ratios can be considered with similar proportions as reported previously,[20] assuming that the age-specific rate of cancer in 2022 would remain constant at the rates estimated in 2020.[42]

However, the actual reflection depends upon final reports, including the impact of COVID-19 time on statistics. The authors expect that the main variation would be in lung cancer cases, a major type of cancer incidence. During the lockdown period, the environmental factors, mainly the air quality,[43] were changed. Furthermore, COVID-19 causes mainly lung infections. Thus, the mortality due to lung cancer and COVID-19 might have impacted considerably, and variance in data may be expected. The co-morbidity due to COVID-19 and other diseases has been observed during SARS-CoV-2 infection.[44] The concerted data would provide an accurate reflection of incidences and mortality for the different types of cancers during and post-COVID-19 pandemic time.

THERAPEUTICS DEVELOPMENT AND CANCER STATISTICS

The progress in developing diagnostic methods and technologies for early cancer detection, as well as monitoring the progress in cancer therapy and developments in new drugs and therapeutics for curing the different types of cancers, directly impact the cancer-related statistical data. Researchers are continuously making efforts towards the development of new methods as well as improvement in existing ones for the detection of cancers.[45] Serological tests,[46] radiodiagnosis,[47,48] ultrasonic methods, magnetic resonance imaging (MRI),[49,50] and positron emission tomography (PET) continuously developed with advances on therapeutic fronts. For example, when Prostate Specific Antigen (PSA) test was introduced in the United States

in the 1990s, it directly impacted and reflected prostate cancer statistics.

Developing improved drugs and therapeutics against cancer is one of the most researched fields.[51] Plant-based herbal drugs,[52–54] molecular inhibitors, and immunotherapeutic biologicals[55] have been considered and used to cure different cancers. Small molecule-based inhibitor drugs are the maximum number of drugs in cancer therapy. The cellular mechanisms and pathologies of the progress of the different cancers constitute the basis of the development of various small molecule-based anticancer drugs,[56] such as nucleoside antimetabolites, topoisomerase inhibitors, mitosis inhibitors, and kinase inhibitors.

Recent efforts have been focused on targeted drug therapy. The targeted therapy is a more practical approach as selected cancer cells are targeted using different specific cancer markers. This reduces the drug dosage and thus decreases the side effects and improves the therapeutic outcome. There are many approaches to targeted therapy, such as using tyrosine kinase inhibitors, monoclonal antibodies, or nanotechnology using targeting moieties.

Tyrosine kinase signaling induces a cascade of molecular events[57] that regulate cell growth, proliferation, migration, and angiogenesis in normal and malignant tissues. Src, Atk, EGFR, HER2/neu, and VEGFR are a few examples of tyrosine kinases that serve as the primary target for a number of small molecules kinase inhibitor drugs as targeted cancer therapy.[58] For example, Imatinib is one of the first small molecule inhibitors approved by the FDA in 2002, which is used for treating chronic myeloid leukemia (CML) and acts by inhibiting BCR-ABL tyrosine kinase protein. Gefinitib is another small molecule kinase inhibitor approved by the FDA for treating solid tumors, such as non-small cell lung cancer (NSCLC), and acts by targeting the EGFR.

Early detection and effective treatment can prove key to completely cure many cancers.

Protein kinase inhibitors have a major presence in FDA-approved drugs during 2015-2020 for cancer treatment. In a summary report,[59] out of 56 drugs approved (2015-2020) for cancer therapy included tyrosine kinase inhibitors (TKIs, 30 drugs), mitogen-activated protein kinase inhibitors (MAPK inhibitors, 3 drugs), cyclin-dependent kinase (CDK inhibitors, 3 drugs), Poly Adenosine diphosphate-Ribose Polymerase (PARP) inhibitors (3 drugs), phosphoinositide 3-kinase (PI3K) inhibitors, (3 drugs), Smoothened receptor (SMO receptor antagonists, 2 drugs), androgen receptor (AR) antagonists (2 drugs), somatostatin receptors (SSTR) inhibitors (2 drugs), isocitrate dehydrogenase inhibitor (IDH) inhibitors (2 drugs), and others (6 drugs).[59] The approval of recent drugs indicated a continuous addition of new small molecule inhibitor drugs to cure different cancers and continued efforts in developing novel kinase inhibitors. We have also been working on the designing and evaluating of kinase inhibitors for the last 20 years.[60–78] This is clear that the efforts will be continued by academia and pharmaceutical companies to develop more potent kinase inhibitors for cancer treatment.

Furthermore, recent nanomedical technologies are revolutionizing research and drug development, particularly the improved drug delivery systems for the improved therapy of cancers.[79–83] A number of delivery vehicles, such as liposomes, niosomes,[84] metal nanoparticles,[85] polymeric materials,[86,87] DNA nanoparticles,[88,89] solid lipid nanoparticles[90,91] natural products-based systems,[92,93] dendrimers,[94] peptides and peptide-drug conjugates,[95–112] fatty acyl prodrugs,[113–116] stimuli responsive metal organic framework (MOF)[117] and many other nano-vehicles[118–121] have been investigated for the cancer management with different drugs.[122–125] Similar approaches have been used for other diseases, such as viral infections.[126–130]

The selected targeting may be through the use of targeting moiety in the nano-formulations[131] or may be stand-alone therapy such as monoclonal antibodies. The antibodies-based therapeutics have revolutionized the cancer treatment regimen, e.g., rituximab is highly effective in the treatment of non-Hodgkin's lymphoma (NHL) and trastuzumab has brought high improvement in breast cancer treatment.[132]

At the molecular biology level science of cancer, microRNAs (miRNA) have been identified. These miRNAs are small (19-25 nucleotides) non-coding RNAs that regulate various genes and thus are involved in the regulation of biological processes, including the biological events in the development of cancer.[133,134] The miRNAs are involved in controlling the genes responsible for drug resistance development, influencing the genes associated with the cell proliferation, cell cycle, and apoptosis.[135] Thus miRNAs serve new targets of study in controlling cancer.[136] Besides that, **l**ong **n**on-**c**oding RNAs (lncRNAs) have been characterized by the development of new RNA-seq technologies. The lncRNA interacts with DNA, RNA, and proteins and influences their functioning through chromatin organization, transcription, and post-transcription processes.[137] Thus, lncRNAs have been implicated in cancer development via involvement in serial steps of cancer progression.[138,139] The miRNA and lncRNA are known to control drug resistance in cancer therapy.[140] Thus, the LncRNAs and miRNAs have emerged as recent targets to control cancer progression and development of effective molecular-level cancer therapeutics in the near future.[141,142]

Furthermore, System Biology, a process of a culmination of different technologies and methods (bioinformatics, pathological studies, data science, diagnostic data, etc.) provides a complete overview of the underlying mechanisms of a biological event. In the case of cancer, System Biology provides the collective details of genomic and epigenetic aberrations in cancer cells that alter the homeostasis of signaling networks within cancerous cells, between cancer cells and in the local microenvironment, and further at the organ and organism level. The overall scenario of conditions in a patient would lead to better-personalized medicine. The System Biology approach would provide an

enhanced efficacy for the management of cancer therapy via a selection of targeted drugs, avoiding drug resistance, and rational combinatorial therapies depending on the patient condition data analysis.[143]

All these concerted efforts are bringing new and improved pharmaceutical drugs and therapeutics for the diagnosis and therapy of different types of cancer, which thus directly impact the cancer burden. The availability of new drugs and medical facilities in respective countries and regions affect the prevalent epidemiology of cancer on the map. Many recent FDA-approved anticancer drugs have been discussed in many reviews;[59,144,145] herein, a brief scenario has been discussed to reflect the relevance of new drug development in cancer management and associated statistics.

The cost of medicines is one of the deciding factors in the availability of therapeutics and the adaptability or applicability of particular medicine for particular cancer. The economic status of patients impacts the continuous dosing for a cure. At the same time, the socio-economic standing of any region or country directly influences the availability of medical facilities for patients.[146] The targeted biological-based therapy (like monoclonal antibodies) has successfully treated different cancers. However, the associated cost of development and maintenance of biologicals draws a line of hurdles in the adaptability of these therapeutics,[132] particularly the economically low-income patients and countries. Small molecule-based chemotherapy is generally a cost-effective regimen. However, it has associated side effects. Cancer therapy may also involve targeted biologicals in combination with regular chemotherapeutic agents. As discussed above, targeted therapy with monoclonal antibodies (mAbs) increases the cost dramatically. For example, colorectal cancer treatment regimens containing bevacizumab or cetuximab cost up to $30,000 (for eight weeks of treatment), compared with about $60 for fluorouracil/leucovorin-based therapy (same weeks).[147] Radiotherapy using radionuclides has been successfully utilized in curing cancers, particularly solid tumors. However, the cost (many antibodies are used as an integral part of radiotherapeutics) and radioactivity exposure-related side effects (to the operator as well as patients) need to be considered for the wide adaptability of this therapy.

Similarly, the radiodiagnosis of cancers has seen a continuous improvement in diagnosis (and therapy monitoring) using different modalities (Radiodiagnostics, MRI, PET, 3D-UltraSound, etc.);[148–155] however, the cost of the instrument (and therefore the respective scan) impacts the usability in low-income countries. For example, the price tag of a PET/CT scanner can range roughly between $1.7 million and $2.5 million. The PET scan is highly accurate and efficient in the diagnosis of cancers, but with costly operating costs.

Future research in cancer diagnosis and therapeutics should consider these points. Besides working on improving the therapeutic potential of the above-mentioned cancer therapy regimens, the researchers have recently oriented their efforts in developing the small molecules (organic chemical drug molecules) that can potentially act as substitutes or replacements for mAb and other biologicals in cancer therapy to mitigate the cost-associated impact on cancer statistics. Below we discuss some treatment options for the most prevalent cancers and challenges in specific populations.[156]

Breast Cancer

Breast cancer is the leading cancer incidence worldwide, with annual 2.26 million reported cases, 11.7% of total cancer cases, and 24.5 % of the cancers in females.[14] It is also the leading cancer in the number of deaths in women (15.5% of annual cancer deaths in females).[14]

Breast cancer is the major reported incidence in female patients.

Triple Negative Breast Cancer (TNBC), characterized by the absence of expression of estrogen receptor, progesterone receptor, and human epidermal growth factor receptor-2 in the cancerous cells, is one of the most malignant and aggressive forms of breast cancer, and it is accompanied by poor prognosis in patients.[157] The use of cytotoxic chemotherapeutic drugs is an established treatment option as TNBC cells are unresponsive to hormonal therapy. The TNBC type of breast cancer is reported to be most prevalent in African countries.[158] It is also contested that data reporting from underdeveloped countries and respective projections of total cancers cases and deaths remain incomplete as the data only report consider the hospital-based cancer reports while people in many regions in underdeveloped and African countries either do not have access to medical facilities or large cases remain unreported (undiagnosed cancer cases) due to socio-cultural settings.[158]

The National Cancer Institute lists a number of FDA-approved chemotherapeutic drugs for breast cancer management (https://www.cancer.gov/about-cancer/treatment/drugs/breast). A few selected drugs are capecitabine, docetaxel, doxorubicin, epirubicin, 5-fluorouracil (5-FU), gemcitabine, methotrexate, paclitaxel, tamoxifen citrate, thiotepa, and many other molecules from kinase inhibitors, cytotoxic anthracyclines, topoisomerase I inhibitors, and nucleosides (Figure 6). The list also includes trastuzumab, an antibody sold with the brand name Herceptin. A variety of therapeutics promises better control of breast cancer.

Because of the lack of receptors expression in TNBC, its treatment remains the most challenging task.[159] The chemotherapeutic options are not so effective in the case of TNBC. The finding of a target is critical in treatment management.[159,160] There is continuous ongoing research for the development of potent new therapeutics[161] or improved chemotherapeutics options for TNBC.[116] In a recent study, the live macrophage-delivered doxorubicin-loaded Liposomes have been reported for effective treatment of TNBC.[116]

Nanomedical formulations help in increased delivery of drugs and mitigate the side effects. FDA has approved the paclitaxel

incorporated into albumin-stabilized nanoparticle formulation for treating breast, lung, and pancreatic cancers.[162,163]

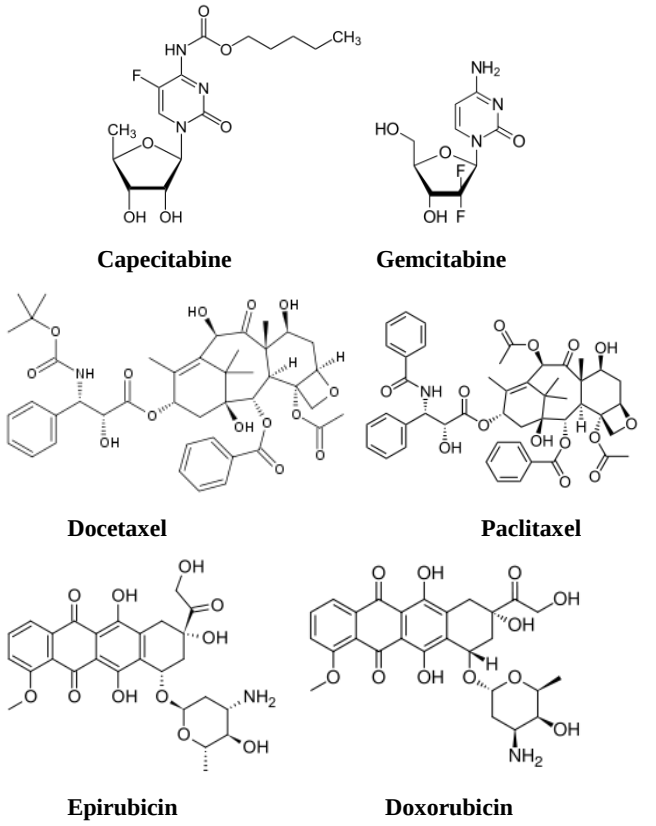

Figure 6. Chemical structures of selected drugs used for breast cancer treatment (and other cancers)

Lung Cancer

Lung cancer continues to be present in all countries and in most regions, with estimated annual incidences of 2.21 million, 11.4% of cancer cases, and a mortality of 1.79 million lung cancer patients every year. Lung cancer is one of the leading causes of cancer-related deaths in men and women.[14] The segregation based on economic development shows no difference in lung cancer deaths in male patients in developed and underdeveloped countries. However, women from developed countries suffer a higher death rate due to lung cancer compared to developing nations. Lung cancer deaths are second to breast cancer in women.[164]

Lung cancer is the most lethal (maximum number of deaths occur due to lung cancer) in both male as well as female patients.

In all countries, cigarette smoking is the main reason for lung cancer incidences and mortality. The ratio of the smoking population is directly linked to lung cancer incidences. It has been observed that as the male smoker population increases, so do men's lung cancer cases.[164] The tobacco control programs bring down the smoking rates peaks, so the lung cancer incidence and mortality decline after an initial rise in respective regions.

Lung cancer cases and deaths have a continuous decline in industrialized countries, including the United States (USA) and the United Kingdom (UK), since 1990. The emerging awareness and reduced smoking habits are one reason for this trend. The availability of medical facilities is another factor in the decline in lung cancer deaths. In other developing countries, cigarette smoking rates are high in both men and women, but in contrast, lung cancer incidences are low. These countries have high mortality rates due to a lack of medical facilities. The lack of medical facilities and unequal access to healthcare facilities lead to delayed diagnosis and treatment of lung cancer. The pattern is aggravated further by environmental contamination and socio-cultural barriers.[164]

The mortality caused by lung cancer is the highest, while at the same time, the FDA boasts approval of a large number of drugs for lung cancer. Table 1 provides a glimpse of several recent drugs approved by the FDA for lung cancer and related malignancies. These drugs are less available or affordable in developing countries but can make a massive difference in lung cancer treatment

Table 1. Recently approved drugs for lung cancer treatment

Drug	Approved for	Approved on
Fam-trastuzumab-deruxtecan-nxki	unresectable or metastatic non-small cell lung cancer (NSCLC)	Aug 2022
Capmatinib	metastatic non-small cell lung cancer (NSCLC)	Aug 2022
Nivolumab	resectable non-small cell lung cancer (NSCLC)	March 2022
Atezolizumab	stage II to IIIA non-small cell lung cancer (NSCLC)	Oct 2021
Mobocertinib	metastatic non-small cell lung cancer (NSCLC)	Sept 2021

Source: FDA > drugs >resources information – approved drugs > oncology

Prostate Cancer

With annual 1.41 million incidences, prostate cancer is the second most prevalent cancer in males (14.1% of the total cancer cases in Men).

Prostate and lung cancers are major reported incidences in male patients

Diagnosis with PSA (Prostate Specific Antigen) helps in the early diagnosis of prostate cancer and fosters better management of the cure of this cancer. The early diagnosis contributes to a wide difference in incidences and deaths for this cancer (Figure 2).[165] The drugs for chemotherapy include docetaxel, mitoxantrone, and cabazitaxel. The hormonal therapeutic agents for prostate cancer include abiraterone or enzalutamide.

Immunotherapy with sipuleucel-T has been employed in treating asymptomatic or minimally metastatic Castration resistant prostate cancer (CRPC).[166] There are 36 drugs approved by the FDA for the treatment of prostate cancer. The complete therapy may involve chemotherapy, including hormonal therapeutics, immunotherapy, and radiotherapy.[167]

COLORECTAL CANCER

Colorectal cancer (CRC) (colon + rectum) accounts for more than 1.85 million cases annually (9.8% of the total cancer cases) and causes an estimated 850,000 deaths (9.2% of total cancer-related deaths) annually. CRC is the third most common cause of cancer mortality worldwide (Figure 1).[168] A recent report has projected about 3.2 million cases of colorectal cancer in 2040, with China and United States as the leading countries in the number of incidences in the next 20 years.[169]

This cancer is associated with the general health of the colon and rectum and partly food consumption habits. The microenvironment in the colon and rectum and inflammatory response have been found to have a keen association with the development of colorectal cancer. The microenvironment comprising immune cells, stromal cells, and the intestinal microbiome collectively creates the processes related to immune responses (suppress or enhance) and generates the inflammatory processes that shape the immune pathogenesis of colorectal cancer.[170] The selected metabolites derived from gut microbiota have also been associated with carcinogenesis of colorectal cancer. Trimethylamine-*N*-oxide (TMAO) is one such metabolite that has attracted attention for its possible role in colorectal cancer.[171] Gut microbiota dysbiosis has been observed with the progression of development of colorectal cancer pathophysiology.[172] The overall healthy microenvironment generation in colon and rectum parts forms the part of preventive measures. Development or supply of general health-oriented gut microbiota through prebiotics or probiotics supplements for the generation of metabolites for the excellent health of colon cells has emerged leading alternative therapy for the colorectal cancers[173,174]

Metal complexes and non-steroidal anti-inflammatory drugs are also used in the main regimen of therapy.[175] The development of anti-inflammatory drugs has opened the potential of natural products (terpenes, terpenoids, flavonoids, and other herbal drugs) for application in the therapy of colorectal cancer. The nanomedical technologies have further shown potential in developing biosensors for cancer biomarkers for the detection of colorectal cancer, besides improving the drug delivery of the above-mentioned drug formulations for colorectal cancer.[176]

LEUKEMIA

Leukemia is the cancer of blood-forming tissues, including bone marrow involving white blood cells. It has different types, such as acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), and chronic lymphocytic leukemia (CLL), which affects different age groups. With an estimated annual 474,519 cases of leukemia contributing 2.5% of total cancer incidences, it is a rare disease that accounts for many incidences. However, leukemias are highly malignant neoplasms with a relatively high mortality rate that accounts for a number (3.1%) of cancer-related deaths. Among different leukemias, AML is found to be a common leukemia cancer in adults; however, it poses a significant threat as it has the lowest survival rate of all leukemias. Despite a smaller number of incidences to total cancer cases, leukemias constitute the leading cause of death due to cancer in persons younger than 39 years old and children.[177] Leukemias (relative to other cancers) are most frequently diagnosed in children below 15 years. In children below 15 years old, AML is detected in 15-20% of patients, while ALL is a major incidence diagnosed in about 76% of all leukemia cases in this age group, with maxima of the rate observed in children less than one year age.[178] The maximum incidences of leukemia cases are in older people. The chance of occurrence, mainly AML, continuously increases with age above 60.[177] The genetic composition profiling supports the variance with age for the occurrence of abnormal genes that may be associated with leukemia cases.[179,180] Unfavorable cytogenetics related to leukemia have been observed with increasing age contributing to the more unfavorable prognosis of leukemia.[180]

The treatment of leukemia involves intensive chemotherapy with anthracyclines (daunorubicin, doxorubicin, etc.) and cytarabine-based regimens, sometime hypomethylating agents, followed by allogeneic stem cell therapy.[181] The nanotechnological advances and prodrug approaches provide tools for improved sustained delivery of anti-leukemia drugs.[182,183] A liposomal formulation of daunorubicin and cytarabine (CPX-351) has been approved for improved leukemia treatment.[184]

As molecular technologies are advancing and understanding of the genetic composition background for the disease is increasing, the treatment for leukemia is improving its regiment drastically. Identifying specific mutations responsible for particular leukemia creates a watchdog for targeting and inhibiting particular mutation expression via molecular genetic tools. For example, AML control can be done by targeting actionable mutations FLT3, IDH1/2, TP53, BCL2, and hedgehog pathways.[185] The immunological and targeted therapeutics, such as antibody-drug conjugates, have emerged in the cure of AML. More advances are emerging in immunotherapies for the development of immune checkpoint inhibitors, new antibody-drug conjugates, bispecific T cell engager antibodies, chimeric antigen receptor (CAR)-T therapy, small biosimilar molecules as an adjuvant for immunotherapy, and the development of AML vaccines for generation of a complete and better cure for leukemia. Gemtuzumab ozogamicin, and glasdegib are antibodies that target CD33 and hedgehog pathway, respectively, and have recently been reapproved for AML cure.[185,186] The cure for leukemias has thus been involving chemotherapeutics drugs, immunological tools, and emerging more role of new genetic technologies.[187]

FUTURE PERSPECTIVE

Cancer estimates with future trends projections (i.e., cancer cases, cancer deaths) and new drug development possibilities are

interdependent factors that have been and will decide the survivorship of patients. Current cancer statistics have been gathered from different sources, particularly hospital-based reports; however, this sourcing can be incomplete due to a lack of access to hospitals for some patients and other socio-economic factors. Furthermore, accurate statistics with the involvement of more agencies and population-based analysis inclusion would provide a better glimpse of the epidemiology of cancer worldwide. The statistics for cancer in the past have shown variance with time, particularly influenced by people's knowledge about this disease and their participation in controlling this menace. Similar trends and behavior have been projected in different studies for the next 20 years, considering the presence of similar contributing factors. However, climate change or environmental alternation has been negated till now. As the world is observing the continuous change in this factor, it might prove to be a more influencing factor on the physiological functioning of human beings (and also expected on the biotic system in general). The population increase would also affect the total cancer data regarding incidences and deaths.

Selected cancer types are expected to be present in an increased number of annual reports, like leukemia. In contrast, a few cancers may follow the declining trend of the past and get reduced to fewer number incidences annually from current lead cases. For example, lung cancer is reduced with increased awareness to stop tobacco smoking.

The efforts for cancer therapeutics development would bring new therapeutics from current laboratory studies to real applications.[188] The involvement of artificial intelligence in drug development with genetic data maps of the different populace,[189] along with progress in personalized medicine, would increase the mean survival of cancer patients.[190] The current survival rate is low (5-7 years) for most cancers, with negligible prospects for a complete cure. Future drug and therapeutics development will need to address the metastatic stages of cancer to improve the statistics.[191] The introduction of applicable nanomedical technologies and bio-immunological therapeutics[55] in clinical applications with targeted theranostics (diagnostics and therapeutics) would provide a healthier living for patients with reduced side effects of current therapies.[192]

Each cancer's pathology is different, requiring the development of different therapeutics (chemo, immune, genetic-based, living style – probiotics etc.) for the respective cancer. Future development of genetic technologies might prove a boon for treating mutation-caused malignancies along with easy vaccine development for selected cancers. Furthermore, recent identification of miRNA and lncRNA association with cancer pathophysiology progression has generated new avenues for development of therapeutics for precision therapy along with potentiation by progress in System biology field.

There is a relationship between progress in diagnostics and therapeutics development with cancer statistics (incidences and deaths). The future better understanding and knowledge of cancer pathophysiology of molecular events would provide a basis for developing advanced and cost-effective diagnostics and therapeutics. The presence of less costly strategies would increase the outreach in the countries with weaker economies and thus influence their cancer-related statistics.

CONCLUSION

The epidemiological distribution of cancer and prevalence of specific cancers in particular regions help policymakers and medical practitioners in decision-making towards the development of medical facilities in general and specific cancer-oriented therapeutics availability for better management of cancer impact over the world. Breast and lung cancers have shown presence throughout the world, with lung cancer being the leading cancer in mortality due to cancers. Tobacco smoking has been associated as the main reason for the prevalence of lung cancer in particular countries and regions; however, the increasing environmental (air) pollution due to industrialization needs thorough consideration for lung or respiratory system-related cancers and other malignancies. The socio-economic status of countries and regions is the one factor for consideration in developing preventive measures and making the essential therapeutics available in the region for proper management of cancer incidences and deaths. African countries are worst impacted due to prevalent social and cultural norms for women and men, which have become a hurdle in implementing medical facilities in some regions.

The continuous efforts for drug and therapeutics development have provided several drugs for the cure of different cancers; however, the complete cure, particularly for advanced stages (metastatic) of cancers, needs further advances with the involvement of lifestyle habit changes for health along with the development of advanced better therapeutics for particular cancer type. Understanding the pathophysiology of specific cancers has helped in better management of respective cancer and assisted in developing new synthetic drugs, immunological biologicals, probiotics (for colorectal cancer), radiotherapeutics, and radiodiagnosis of cancer. New advances in science, like progress in the nanomedical technologies using nanoparticles, liposomes, solid lipid nanoparticles, niosomes, metal nanoparticles, polymeric nanoparticles, natural products-based nanosystems, and other nanoconjugates have revolutionized the drug delivery systems, with major emphasis on cancer drugs delivery as well as new biosensors development for early diagnosis of cancer biomarkers. The progress in different molecular drugs and therapeutics would provide a scenario of higher life expectancy and healthy living for cancer patients.

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CONFLICT OF INTEREST STATEMENT

The authors declare that there is no related conflict – academic, financial, or otherwise for publication of this work.

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