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Cancer overview and challenges of rare cancers.

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Abstract

A cluster of related diseases collectively called cancer causes high morbidity and mortality in humans. More streamlined and up to date cancer statistical data resource for use of health professionals and patients is required. This overview gives a glimpse of what causative factors are involved in the pathogenesis of cancer malignancies, how new drugs are being identified from various sources, how therapeutic methods are evolving and tilting towards targeted cancer therapy. The need for paying attention to rare cancers, making available rare cancer pathological tissue samples for research and special arrangements for rare cancer clinical trials are explained.

Key words: Biopharmaceuticals, cancer, Carcinogen, Drug discovery, Proteomics, Rare cancer, Targeted therapy

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INTRODUTION

Uncontrolled cellular proliferation due to underlying compromised cell division mechanism causes several distinct diseases, collectively known as cancer. The resulting tumors are of two kinds, the benign and the malignant and are the consequence of unchecked cell division and growth in any given tissue in organisms including human. Malignant tumors that proliferate and spread aggressively are classified cancerous, whereas benign tumors are neither aggressive nor invade or spread to other tissues (Kleinsmith, 2006; Weinberg, 2014). A myriad of related, non-contagious diseases amounting to nearly two hundred distinct well defined debilitating conditions are grouped under cancer. Though human and other organisms are exposed to a plethora of environmental and other factors, the cancer pathogenesis is confined to a select number of susceptible individuals in a given population. This property of cancer depends on the resistance the body offers against pathogenic factors, age, nutritional state of the individuals, compounded with the virulence of invading cancer causing microorganisms and the degree of exposure to cancer causing agents. During the process of aging, spontaneously occurring somatic cell mutations progressively accumulate throughout life in an individual, which can ultimately lead to cancer as well (Martincorena and Campbell, 2015).

Researchers have identified more than 500 altered genes that can play a role in tumor development (Cancer and the environment, NIH, 2003). Mutations in several regulatory genes interrupt cellular homeostasis leading to uncontrolled cellular growth. Tumor suppressor genes (antioncogenes) are regulatory elements whose expression products regulate and streamline controlled cell growth. Proto-oncogenes when mutated turn into oncogenes whose protein products can cause apoptotic cells to survive and proliferate to become tumor. Similarly certain DNA repair gene mutations could result in compromised cell growth regulation. Normal cells during proliferation undergo several mechanisms which reign in any uncontrolled growth. When normal cells fail to conform to this quality control, the cells are channelled to the process called apoptosis or programmed cell death. On the other hand, cancerous tumor cells with their own modified genetic make up defy the apoptotic quality control. Cancer cells unlike normal cells evade their attachment to extracellular matrix (ECM) molecules. This distinct characteristic of lack of ability of cancer cells to bind to ECM, paves way for them gaining access to vascular and lymphatic systems. Such transformed cancer cells turn metastatic and invade other organ, near and away, and as a result disseminate and spread cancerous cells causing metastatic tumors. (Paul *et al.*, 2019)

Resources for cancer statistics

Many countries have organized cancer registries that serve as information resources which collect, store and manage the data. Often interlinked, the population and hospital based cancer registries are distributed in various centres. Under the National Cancer Registry Programme, ICMR collects and

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provides data on patterns of cancer in different parts of India and the estimated incidence of cancer in the country. Three population based cancer registries and three hospital based cancer registries were originally established in 1982, but now have grown to become 33 and 101 registry centers, respectively (National Centre for Disease Informatics and Research, 2017). NCRP is modelled on the more robust National Cancer Institute's Surveillance, Epidemiology and End Results program of the US (Mohanty and Bilimoria, 2014).

Of the few hundred distinct types of cancers, a handful of cancer types predominate the human cancer arena. Mammary, cervical, oral-esophageal, lung, gastric-colorectal and prostate cancers are more common than other cancer types. These common cancers constitute about 50% of cancer in India according to statistical data from NCRP. Breast cancer is the most common cancer in women accounting for 14% of all cancer, while oral cancer is the most common cancer type in men at 16% (Cancer Samiksha,2017).

Causes

Various factors are identified to be the etiological cause of tumor development, encompassing environmental factors such as natural and synthetic chemicals, microorganisms, genetic factors as well as idiopathic referring to causes of unidentified origin (Cancer and the environment, NIH, 2003). There are 248 total numbers of listed substances or classes of structurally related chemicals or agents identified to be carcinogens. Of these identified agents, 62 are known to be a human carcinogen and 186 are listed have the potential to be human carcinogens (14th Report on Carcinogens, National Toxicology Program, 2016). There is a wide variety of natural, synthetic and physical agents that can cause cancer. Tobacco, alcohol, aflatoxins, ionizing radiation like UV and X ray, viruses, bacteria, pesticides, benzenes, asbestos, silica dust, dioxins, polycyclic aromatic hydrocarbons, arsenic, beryllium, vinyl chloride and benzidine-based dyes,(Cancer and the environment, NIH, 2003).**(Table 1)**. Certain pollutants have potential to interact with one another and with genetic materials. Carcinogens can cause epigenetic alterations, damage DNA, disrupt hormones, inflame tissues, or switch genes on or off (O'Hagan, 2014). A few lifestyle factors, such as various forms of tobacco usage, sedendary life with reduced or no physical activity, nutrition factors, and obesity have the potentiating effect on cancer deaths (Balhareth *et al*., 2019).

Cancer proteomics

The impact of the nascent field of clinical proteomics in human health is yet to come of age. As of now its implication in patient management and decision-making seems low (Maes *et al*., 2015). However the scope for precise application of the evolving area of proteomics in the future on cancer patients is enormous. Normal cells, during the cell division, undergo a series of cell cycle checkpoints before mitotic cell division and distribution of the genetic materials to the newly divided cells. As a response to genotoxic stress, cells activate these cell cycle checkpoints, thus preventing further progression of the cell cycle and initiate DNA repair. If the checkpoint mechanisms identify extent of DNA damage is beyond their repair capacity, further signalling pathways are activated to induce apoptotic processes and thus eliminate potentially dangerous mutated cells in the body. This entire signalling network inside the cell, called the DNA damage response (DDR), is very tightly controlled and involves regulation at the transcriptional, post-transcriptional, and post-translational levels during the life of a cell (Reinhardt and Schumacher, 2012; Reinhardt and Yaffe, 2013;Dietlein *et al*.,2014). The emerging field of cancer proteomics offers insight into the altered environs inside and on the surface of malignant cells. DDR repair hubs are often found to be altered in cancer cells. Conservative estimate is that over 550 different genes or their protein products are identified and implicated in transformation of healthy cells into cancerous ones. Precisely targeting these regulatory hub genes and their protein molecules is possibly challenging yet a viable approach (Dietlein *et al*., 2014).

Chemotherapy and targeted therapy

Chemotherapy, a specific yet not focused approach, is currently a staple in cancer management, and is considered to be a blanket treatment method. Often used standard chemotherapeutic drugs are cytotoxic not only to rapidly dividing tumour cells but also to normal cells including the lymphocytes of the immune system in the body, causing unpleasant side effects (van der Most *et al*., 2005). Targeted therapy on the other hand is aimed at specific target molecules of tumour cells. Thus, focusing on tumour specific molecules result in interference with the tumour cell function and ultimately lead to cell death, leaving normal cells unaffected. Thus targeted therapy, aimed either at the cell surface or intracellular molecules offers a far fetched precision approach in medicine. Signal transduction inhibitors, gene expression modulators, apoptosis inducer, angiogenesis inhibitor, hormone therapies, toxin delivery are examples of this approach. (Lake and Robinson, 2005; van der Most *et al.,* 2005)

Phytochemical drugs in cancer therapy

In general disease scenario, many of currently used synthetic drugs for various diseases are based on naturally occurring plant and animal products.

Table 1. Short list of selected environmental carcinogens

Physical and chemical carcinogens	Cancer causing organisms
X-ray (CT scan. Large amount radiation in multiple exposures) **Ultra violet radiation** **Radon radiation** **Bisphenol A** **Formaldehyde** **Benzene** **Perfluorooctanoic acid** (Teflon) - (Used in polytetrafluoroethylene non-stick cookware coating) **Tobacco** (Smokers and secondary smokers with high aryl hydrocarbon hydroxylase enzyme activity metabolize tobacco smoke's benzopyrene into other highly carcinogenic agents) **Alcohol** **Excess iodine** **Vinclozolin** - Leydig cell testicular cancer **Dioxins** **Arsenic** **Cadmium** **Ethylene oxide** **Silica dust** **Asbestos**	**Viruses** Hepatitis B virus Epstein-Barr virus Papilloma virus HTLV-I virus Rous Sarcoma virus **Bacteria** *Helicobacter pylori* - gastric mucosal cancer and gastric adenocarcinoma. *Schistosoma haematobium* - squamous cell bladder cancer **Fungi** Aflatoxin B1 - produced by *Aspergillus flavus* Cyclochrotine - *Penicillium islandicum* **Helminths** *Opisthorchis viverrini* *Clonorchis sinensis*

Table 2. Short list of selected anti-cancer drugs

Microbial anti-tumour compounds	Plant-derived anti-tumour compounds
Aromatic polyketides (Anthracyclines) Daunorubicin Doxorubicin (Adriamycin) Epirubicin Pirirubicin Idarubicin Valrubicin Amrubicin **Glycopeptides, Non-ribosomal peptides, Anthracenones** Bleomycin Phleomycin Actinomycin D (dactinomycin) Mithramycin Streptozotecin Pentostatin **Quinones, Polyketides, Indolocarbazoles, Polyketides** Mitosanes - Mitomycin C Enediynes - Calicheamycin Indolocarbazole glycosides - Rebeccamycin Macrolide lactones - Epotihilones **Nucleosides, Halogenated compounds** 2-deoxycoformycin (Pentostatin) Salinosporamide A	Vinblastine (Velban) Vincristine (Oncovin) Etoposide Teniposide Taxol (Paclitaxel) Navelbine (Vinorelbine) Taxotere (Docetaxel) Camptothecin (Camptosar, Campto) Topotecan (Hycamtin) Irinotecan **Marine-derived anti-tumour compounds** Cytarabine (Cyto star) Pederin Theopederins Annamides Trabectedin (Yondelis, Ecteinascidin 743) Aplidine **Tumor targeted drugs** Tyrosine proteinkinase inhibitors - Imanitab, Nilotinib EGF receptor inhibitor - Gefitinib, Erlotinib Angiogenesis inhibitors - Bevacizumab Proteasome Inhibitor - Bortezomib Unarmed MAb - Tituximab, Trastuzumab

Widely used hirudin-like synthetic anticoagulant peptides are based on leech protein, while small molecule quinine and its synthetic counterparts used in malaria treatment are based on an alkaloid from the bark of cinchona tree. In both cases traditional native use of these drugs in specific ailments has led to successful disease management throughout the world even today.

The estimated potential plant extracts which could be obtained from the higher plants in the world's tropical forests is about 750,000 (Mendelsohn and Balick, 1995). Small molecules and macromolecules alike have been in focus for fishing out clinically useful therapeutic agents from various sources including plants. Molecules with molecular weight less than 2.5 kD have been synthetically made for use in cancer treatment (Roessner and Scott, 1996). A number of compounds with anti-tumour activities identified to be of several structural classes such as anthracyclines, enediynes, indolocarbazoles, isoprenoids, polyketide macrolides and non-ribosomal polypeptides are from various biological sources **(Table 2).** They include a number of anti-tumour drugs including paclitaxel (Trade name Taxol) (Rawls, 1998; Raskin *et al.*, 2002) used in lung, ovarian, breast, cervical, pancreatic and other types of cancers. Being one of the few successful chemotherapeutic phytochemical drugs, Abraxane (paclitaxel), is now in clinical use in India (Biocon, 2018).

A wide variety of plant derived biopharmaceutical products usually in the form of crude cocktail extracts are still in use in native Indian medicine systems. Considering the wealth of plant biodiversity in India coupled with existing traditional knowledge of them, if and when systematically harnessed, could possibly unearth many new phytochemical compounds that could likely and potentially be a panacea for cancer (Demain and Vaishnav, 2011).

Combinatorial chemistry and drug discovery

Combinatorial chemistry is a laboratory level or industrial scale chemical synthetic method. Using this computerised, automated synthetic method can synthesise thousands of small molecules and peptides in a single process creating a library of molecules in very short duration. Combinatorial library methods have the ability to generate hugely diverse chemical libraries from phage-display, yeast-display, bacteria-display, mRNA-display, One Bead One Compound, DNA Encoded Chemical Libraries, and solution phase mixture libraries (Liu *et al*., 2017). As a result, a large range of linear or macrocyclic chemical molecules like peptides, non-peptide oligomers, peptidomimetic compounds, small-molecules, and natural product-like organic molecules have been generated (Liu *et al*., 2017). Screening these diverse libraries of molecules *in vitro* for anticancer activities, new molecules of potential therapeutic values are being discovered and used in further downstream investigation such as diagnosis and treatment of cancer patients. Unique cell surface receptors of prostate cancer, T-cell and B-cell lymphoma, ovarian and lung cancers have been identified and investigated (Aina *et al*., 2007).

Rare cancers

Rare diseases in general are defined by their infrequency of occurrence in human population. Diseases affecting fewer than 100 patients per 100,000 population (less than 1 in 1000) are described as rare diseases as defined by the World Health Organization. Similarly certain rare diseases with fewer than 2 patients per 100,000 population are referred to as ultra rare diseases. Globally, thus far over 7,000 rare and ultra rare diseases have been described. (Rajasimha *et al*., 2014; Gammie *et al*., 2015) Some 'uncommon' cancer types are grouped under 'rare cancer' (Gammie et al., 2015; Mallone *et al*., 2017; National Policy, India, 2017). This group of rare cancers account for 22% of all cancer diagnosed worldwide (Gatta *et al*., 2010; Greenlee *et al*., 2010). Rare cancers, as with non-cancer rare diseases, are often misdiagnosed and grouped with other common cancer types due to overlapping presentation of symptoms. Lack of clinical expertise on rare cancer amplifies the end result. When patients become refractory to the type of treatment given, precious time is lost and the rare cancer progresses to the next stage during the intervening period (Miller 2010; Gatta *et al*., 2011). Pharmaceutical industry, considering the very limited end user patient population for their drugs and limited prospect of return on their investment, act oblivious to rare cancers.

For quality understanding of rare cancers, the basic requirement and necessity are rare cancer tissue and cell samples for lab studies. Molecular genetic analyses have been hampered, as with any rare and ultra rare diseases, by the limited accessibility of suitable rare tumor samples. A centralized collection and distribution of tumour samples from rare cancers and linkage to cancer registries is paramount. This resource infrastructure would offer the chance for pathologists to improve their horizons and scientists to improve the understanding of the molecular mechanisms of rare cancers, and its positive impact on the outcome of clinical diagnosis (Pillai and Jayasree, 2017).

Clinical trials

In addition to many previously reported cancer types, more and more new forms of cancer are being reported. Cancer being a heterogeneous group of distinct diseases, diagnostic and treatment procedures ought

to be disparate in order to successfully overcome the symptoms and gain recovery. Promising new cancer drugs discovered by traditional methods or combinatorial synthetic methods after successful completion of laboratory level cellular and animal studies, are trial tested on select patient populations. Clinical trials like these are conducted in a phased manner with progressively increasing number of patients in multiple health centers in wider geographic area. The National Institutes of Health's 'ClinicalTrials.gov' database provides the most comprehensive information from its searchable database for clinical trials including cancer drug clinical trials for over 300,000 trial studies in 209 countries (ClinicalTrials.gov, NIH). Drugs originally developed for other diseases and sometimes 'repurposed' for cancer treatment also undergo clinical trials and are listed in the clinical trials database.

Recruiting patients for clinical trials in case of common cancer types are usually comparatively less cumbersome than the rare cancer types. Rare cancer patients being painfully small in number, in addition to delayed diagnosis, their very small numbers in a given geographic area often become a limiting factor in clinical trial recruitments. To circumvent these issues International Rare Cancer Intiative (IRCI) facilitates international collaborations to conduct international clinical trials for rare cancer patients (Keat *et al*., 2013).

CONCLUSION

Uncontrolled harmful cell growth is the hallmark of cancer. Heterogeneous group of cancer diseases is a major health challenge. In India, 14% in women and 16% in men are identified to be affected by breast and oral cancer, respectively. Understanding cancer disease mechanism is paramount in identifying and designing new drugs, and in prudent employment of the phytochemical drugs and other natural sources.While the burden of managing large common cancer population is enormous, it is still more difficult to manage rare cancer population since many rare cancers do not have drugs. A strong multi-pronged national policy aimed at uniting all the stakeholders in terms of quality cancer epidemiology, development of new diagnostic methods, drug development, clinical trials and innovative clinical approach in patient care might mitigate the challenges faced by not only general cancer population but as well as benefit rare cancer patients.

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