Introduction
Cancer is a multi-stage disease or condition in which there is an uncontrolled growth of cells, which can invade and spread to distant body parts. According to WHO (World Health Organization), cancer is among the leading causes of morbidity and mortality worldwide and the new cases are expected to increase by 70% in the next two decades. As per the records of 2012, cancer accounted for 8.2 million deaths with lung cancer contributing to it in first place, followed by liver, stomach, colorectal and breast cancers (W.H.O., 2015).

A brief history of landmarks in cancer research
The earliest written description of cancer is found in the Edwin Smith Papyrus (referenced a breast tumor); written approximately 3000 BC and the Ebers Papyrus, dating to 1500 BC (referenced a soft-tissue tumor, and cancers of the stomach, uterus, skin, and rectum). Until the 19th century, knives, salts, cautery and arsenic paste were used by the Egyptians to treat tumors. The Indians and Chinese depended on herbal medicine as well as metals like iron, mercury and copper in various forms for more than 3000 years. Hippocrates (460-375 BC), the father of medicine used the terms “carcinoma” and “carcinos” which in Greek meant “crab”. He and his disciples had a vast knowledge about the different types of superficial and deep carcinomas and used various lotions, cautery and deep tumors were removed with a knife. He considered only palliative treatments to aggressive breast and colon cancers (Hajdu, 2011a).

Aulus Celsus (25 BC-AD 50), a Roman physician in his book De Medicina described about cancers of the spleen, liver, colon and stomach and recommended early surgery. He translated carcinos to the Latin word cancer. Pliny the Roman (AD 23-79), in Materia Medica compiled various remedies for internal use. His prescription of a boiled mixture of ash of sea crabs, egg white, honey, and powdered falcon feces was widely appreciated. Aretaeus (AD 81-138) also made comprehensive description about various cancers. Galen (AD 130-200) is well known for the humoral theory and many dogmatic theories (Hajdu, 2011a).

Lanfranc (1252-1315) founded French surgery. Henri de Mondeville (1260-1320) and Guy de Chauliac (1300-1368), two French physicians rejected the almost 1000 year old Galen theories which led to advancements in treatment of cancer. Paracelsus (1493-1541) introduced chemotherapy by administering various metals like lead, zinc, copper, arsenic etc. internally (Hajdu, 2011b)

Johannes Scultetus (1595-1645), a German surgeon treated breast cancer by mastectomy and cauterization. He illustrated his findings and surgical methods in Armamentarium
Chirurgicum. Deshaies Gendron (1663-1750), another French surgeon gave insight into transformation of vascular, glandular and other solid body structures to cancers as well as about metastasis. Much advancement in pathology, surgery and treatment of cancer were made during the 1600s and 1700s (Hajdu, 2011b).

Astley Cooper (1768-1841), an English surgeon first identified fibroadenoma of breast as a distinct benign tumor. In 1829, a French gynecologist Recamier (1774-1852) introduced the word “metastasis” and had successfully treated many breast cancer cases. He believed that heredity has a disposition in breast cancer development (Hajdu, 2012a).

In mid 1800s, physicians and surgeons found that microscopy might be beneficial in diagnosis and biopsy. The introduction of cell theory by Theodor Schwann (1810-1882) in 1838 revolutionized the biological sciences. In the same year, Johannes Muller gave a detailed insight into various types of cancers, its invasive potential and tumor necrosis. He is always remembered for his significant contributions to histology and pathology as well as for establishing the cellular nature of benign and malignant tumors (Hajdu, 2012a).

Julius Vogel (1814-1880) published a comprehensive book on pathology in which he had histologic sections of carcinomas of various parts like the liver, breast, uterus, lung and testis. In 1848, Henry Bence Jones (1814-1873), an English physician discovered proteinuria in plasma cell myeloma which persisted as the solitary biochemical test for cancer till the 1970s. John Birkett (1815-1904) presented the terms lobular carcinoma, infiltrating lobular carcinoma and lobular carcinoma in situ. James Paget (1811-1899) described about a type of breast carcinoma spreading to the skin and the nipple, which later started being known as the Paget’s disease (Hajdu, 2012a).

Two major landmarks in cancer treatment were made in the 19th century by the discovery of X-ray by Rontgen in 1895 and radioactivity by Pierre Curie, Marie Sklodowska Curie and Antoine H. Becquerel (Hajdu, 2012b).

The early 1900s showed advances in chemotherapy, identification of environmental carcinogens, influence of hormones in cancer, performing mammography, identification of DNA etc. From 1970 onwards, much emphasis was given to cancer research which led to identification of oncogenes, tumor suppressors, and viruses causing cancer. Various screening methods were developed like MRI (magnetic resonance imaging), tomography, immunohistochemistry etc. The crusade against neoplasia has helped to successfully treat and reduce the cancer mortality, which was possible due to the findings and contributions made by eminent physicians, surgeons and a multidisciplinary setting including researchers, oncologists, radiologists etc. (Hajdu et al., 2015)
Hallmarks of cancer
Research advancements made in the past decades at the molecular, cellular and biochemical levels has resulted in the reconceptualization of cancer. A few of the acquired traits by the cancer cells make them more complex and difficult to treat. These characteristics include self-sufficiency in growth signals and insensitivity to anti-growth signals, limitless replication potential, sustained angiogenesis, escaping apoptosis, invasion and metastatic potential. Almost all types of cancer share these traits (Hanahan and Weinberg, 2011, Hanahan and Weinberg, 2000).

![Fig.1.1. Hallmarks of cancer](image)

The normal cells have a controlled cell cycle which is regulated carefully by various growth and anti-growth signals. Cancer cells deregulate these mechanisms and maintain their own proliferative signals. They may produce growth factor ligands themselves or may send signals to stimulate the normal tumor-associated stromal cells which reciprocate by supplying various growth factors to the cancer cells (Bhowmick et al., 2004).

In order to sustain the growth promoting factors, the cancer cells also should evade themselves from the growth suppressors as well. Numerous tumor suppressor genes have been studied and validated. Two of them, RB (retinoblastoma-associated) and TP53 (tumor
protein p53) proteins, play key roles in cell senescence and apoptosis. The RB protein integrates cellular signals from diverse extracellular ligands and decides whether or not a cell should proceed through its growth and cell division cycle and if loss of its function may lead to cancer (Burkhart and Sage, 2008, Hanahan and Weinberg, 2011). In response to abnormal signals, TP53 gene can halt cell cycle until the conditions are normalized or alternatively it can induce apoptosis if the DNA change is irreparable (Evan and Littlewood, 1998).

Another trait of cancer cells is their ability to evade apoptosis or programmed cell death which is a natural cell barrier to cancer development. The pro- and anti-apoptotic members of the Bcl-2 family are well known regulators of apoptosis. Cancer cells exhibit a multiplicity of mechanisms to escape apoptosis some of which include loss of TP53 function, increased expression of anti-apoptotic factors, downregulation of pro-apoptotic factors etc. (Adams and Cory, 2007, Hanahan and Weinberg, 2011).

Normal cells are able to pass through a limited number of cell cycle due to senescence (a viable but non-proliferative state) and then crisis phase (or cell death). Cancer cells can circumvent these barriers which will result in immortalization and unlimited replicative potential. Telomeres present at the chromosomal end protect the normal cells’ DNA from end to end fusion. These fusions threaten the cell viability and the length of the telomeric DNA is accordingly regulated so that after a limited number of cell cycles the telomeres are eroded and cell crisis happens. The DNA polymerase enzyme, a telomerase, which adds the telomere at the DNA ends, is expressed significantly in cancer cells which help them to counter the telomere erosion. Telomerase activity is almost absent in non-immortalized cells (Hanahan and Weinberg, 2011).

Cancer cells or tumors also require oxygen and nutrients to sustain. They are capable of sprouting new blood vessels by activating an “angiogenic switch” which is again regulated by pro-and anti-angiogenic members. Pro-angiogenic factors like VEGF (Vascular endothelial growth factor) and fibroblast growth factor (FGF) are upregulated in cancer cells (Folkman and Shing, 1992). TSP-1 (thrombospondin-1), endostatin and angiostatin are few natural barriers to angiogenesis. Studies showed that deleting the genes encoding these inhibitors has resulted in tumor progression in mice (Nyberg et al., 2005).

Through complex communication between the tumor cells, stromal cells and its microenvironment, tumor cells are able to invade and metastasize (Ost et al., 2015).

Recent findings also propose that apart from the above mentioned acquired characteristics, the cancer cells are able to reprogram the cells’ metabolism to fuel the growth. Another trait
is the ability of cancer cells to evade from the attack of immune cells and thereby enhance tumor progression (Hanahan and Weinberg, 2011).
These hallmarks have been the basic platform for most of the advancements in cancer research and have helped in uncovering and understanding cancer at a much deeper level.

**Breast cancer**
Breast cancer is the most frequent cancer among women with 1.67 million new cases estimated in 2012 (GLOBOCAN, 2012). Even with advancements in diagnosis and treatment the number of new breast cancer cases is alarmingly increasing worldwide. Risk factors of breast cancer involve increased exposure to hormones (endogenous estrogens, exogenous menopausal hormone therapy, oral contraceptives), lifestyle, genetic and environmental factors (Dossus and Benusiglio, 2015)

Types of breast cancer (C.B.C.F., 2014)
1. **Non-invasive or In Situ breast cancer** represents the type which will be confined to lobules or milk ducts. There are two sub-types.
   a) Ductal Carcinoma in situ (DCIS), where the cancer cells will be located in the lining of milk ducts and doesn’t invade the surrounding tissue.
   b) Lobular Carcinoma in situ (LCIS), where the cancerous cells will be located in the lobules of breast and does not invade the surrounding tissue.
2. **Invasive breast cancer**
   a) Invasive ductal carcinoma (IDC), the most common form of invasive type (around 80%) in which the cancer originates in the milk ducts and then invades the surrounding tissue and metastasizes through the lymph nodes. IDC have various subtypes like tubular, medullary, mucinous, papillary and cribriform.
   b) Invasive lobular carcinoma (ILC), comprising around 10% of the invasive type, originates in the lobules of the breast and metastasize through the lymph nodes.
3. **Inflammatory breast cancer**, the most aggressive and rarest form and accounts for about 1-3% of all breast cancer types. This presents as infection of breast tissue and typical characteristics of breast cancer, like the appearance of lumps in breast may be missing. Hence it becomes difficult to diagnose.
5. **Phyllodes tumors**, in which the tumor cells grow like leaf-patterns in breast and accounts for only less than 1% of all breast tumors.
Challenges in breast cancer treatment

The heterogeneity of breast cancer makes it difficult to treat. The main therapeutic strategies for breast cancer treatment have been focused on estrogen receptors (ER) and human epidermal growth factor receptor 2 (HER2). Majority of breast cancers (about 80%) are Estrogen receptor positive (ER\textsuperscript{+ve}) which make them susceptible to hormonal treatments after surgery. Out of this, around 60% are progesterone receptor positive also (PR\textsuperscript{+ve}). But hormonal therapy has adverse effects like hot flushes, weight gain, sexual dysfunction, decreased bone mineral density (BMD), osteoporosis and pathologic fractures, or musculoskeletal symptoms. Most of these symptoms are due to estrogen deprivation. Even after a long term therapy of 5 years with the endocrine agents, the risk of recurrence remains.

Triple negative breast cancers are a more aggressive type as they lack estrogen receptors, progesterone receptors and HER2 (human epidermal growth factor receptor 2/ neu). They do not respond to hormonal therapies of HER2-targeted therapies due to lack of the respective receptors. Hence, patients with triple negative cancer has poor prognosis. Breast cancers with BRCA1 mutations are also presented as triple negative phenotype (Sledge et al., 2014).

Treatment of breast cancer (A.C.S., 2015)

Chemotherapy of breast cancer is based on different factors like tumor type, grade, receptor status, size of tumor etc. The main treatment options are:

1. Surgery
2. Radiation therapy, given generally after the surgery.
3. Chemotherapy with drugs such as Cisplatin, Vinorelbine, Capecitabine, Doxorubicin, Docetaxel, Gemcitabine etc.
4. Hormonal therapy
   a) Selective estrogen receptor modulators- Tamoxifen, Torimefene
   b) Selective estrogen receptor down regulators- Fulvestrant
   c) Aromatase inhibitors- Letrozole, Anastrozole, Exemestane
   d) Ovarian ablation/oophorectomy - to shut down or permanently remove the ovaries, which are the primary source of estrogens.
5. Targeted therapy
   Drugs targeting the HER2/neu protein (human epidermal growth factor receptor 2 or proto oncogene Neu) have been developed. Trastuzumab (Herceptin), Pertuzumab, Ado-trastuzumab emtansine and Lapatinib are a few examples.
6. Bone-directed therapy, where drugs are given to reduce the skeletal complications (pain and fracture) induced by metastatic breast cancer. Bisphosphonates and Denosumab are examples.

**Adverse effects**
Side effects of these chemotherapeutic agents include cardiomyopathy, neuropathy, chemo brain, acute myeloid leukemia, menstrual changes, alopecia, osteoporosis etc.

**Targeted therapies**
Hormonal receptor positive (HR\(^+\)) breast cancers are driven by the estrogen pathway. Binding of estrogen to the receptors leads to genomic action through various transcription factors like ERE (estrogen responsive element) and other coactivators. But apart from this, the membrane bound estrogen also mediates some non-genomic effects through various signaling molecules such as G-protein, PI3K, ras etc. resulting in cell proliferation and survival. Hence, these pathways could be targeted for the treatment of breast cancer (Mohamed et al., 2013). Other pathways being targeted include the Src, IGF-1R, FGFR, and MAPK pathways (Fig.1.2)
Deregulation of the PI3K/AKT/mTOR pathway is an important mechanism of hormonal resistance and hence inhibitors of the same are also gaining attention. Rapamycin analogs (eg: everolimus) were the first of its kind in clinical trials and has been proven beneficial along with an aromatase inhibitor in hormonal resistant cases and in post-menopausal women who are HR\(^+\) and HER2\(^-\) (Baselga et al., 2012). Several other drugs like inhibitors of panisoform of PI3K and selective PI3K\(\alpha\) inhibitors are in clinical trials.
**Fig. 1.2. Estrogen receptor pathway and targets for treatment**

**Prevention of breast cancer**

Recent advancements in breast cancer research focuses on its prevention using the existing estrogen receptor targeted therapies. Tamoxifen has been found to reduce the risk of breast cancer by one-third in clinical trials conducted in pre- and post-menopausal women. Clinical trials conducted with exemastane and anastrazole also showed a significant reduction (about one half to two thirds) in invasive breast cancer risk. But no survival benefits were reported from these studies due to non-compliance of the patients and short follow-ups.

Prophylactic mastectomy has also been considered as a means of reducing breast cancer risk and could be beneficial for high risk women with BRCA mutation carriers.

Changes in lifestyle like increasing physical activity, prevention of obesity, dietary modifications etc. has been advocated for breast cancer prevention, but still an efficient and well-accepted approach remains elusive (Sledge et al., 2014).
References


