Chapter 1

Introduction

Cancer:

Genetic and non-genetic variations that are influenced by mainly environmental factors are responsible for a switch on or off of specific genes. Due to this phenomenon neoplastic transformations or abnormal cell growth occurs. Abnormal cell growth defines the deadly disease of the century that is "cancer". Still now there is no confirming data about early stages of cancer progression, environmental factors and internal signals that trigger genetic and non-genetic information. According to World Cancer Report 2008, "the global burden of cancer doubled between 1975 and 2000 and is expected to double again by 2020 and nearly triple by 2030". Nowadays, breast and cervical cancer are very common among women of all age groups. Early detection, implementation of vaccination and effective treatment programs can reduce the burden of cancer successfully.

1.1.1 Breast cancer:

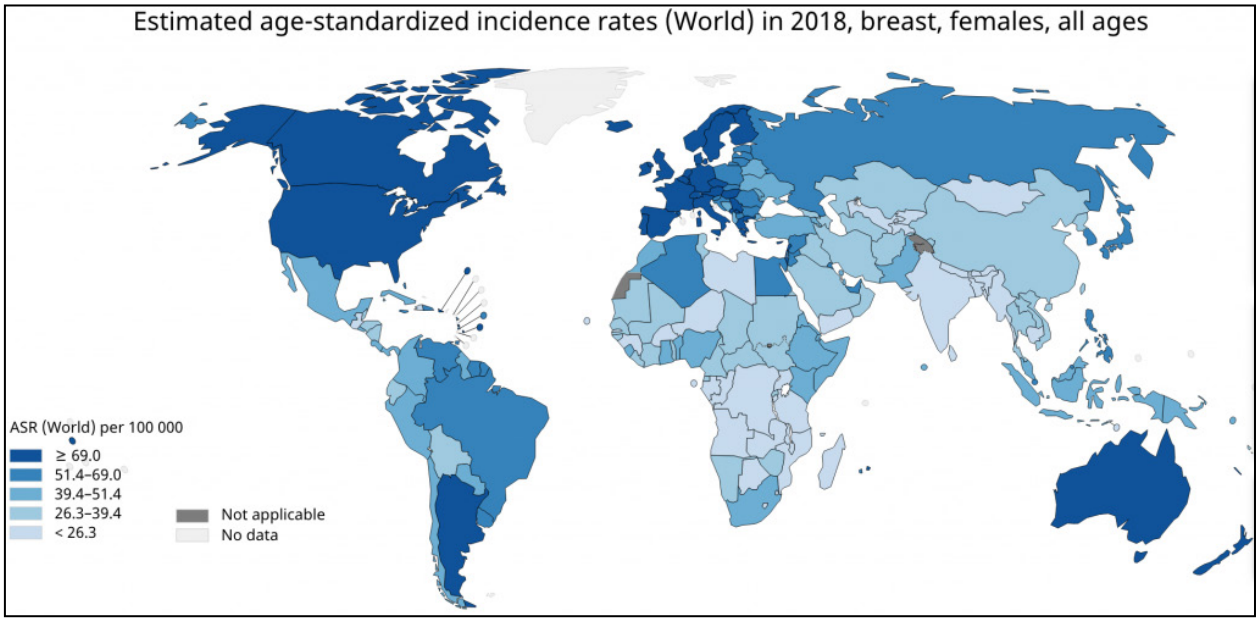

Fig 1.1: Representation of the estimated age-standardized incidence rates of Breast cancer
Source: http://mammalive.net/research/global-breast-cancer-incidence-2018/

Breast cancer occupies the 5th position for the cause of death among the other types of cancer. In developing countries the rate of occurrence of breast cancer in woman is very common. Still now, the exact cause of breast cancers is not known to us. Most probably the cause is related to variations in the genetic material (DNA) in our cells which can be attributed to our lifestyle, aging, alcohol use, Post-menopausal hormone therapy (PHT), etc. People with

BRCA1 and BRCA2 gene mutation are at the risk of developing breast cancer (Gage et al., 2012). Women having dense breast tissues are more susceptible to breast cancer and it is very difficult to diagnose in early stages. Women with high estrogen and progesterone levels have higher chances of tumor development (Tian et al., 2018).

1.1.2 Cervical cancer:

In low and middle income countries the occurrence rate of cervical cancer is remarkably high. According to W.H.O report 266,000 women died of cervical cancer in 2012 (World Health Organization 2016).

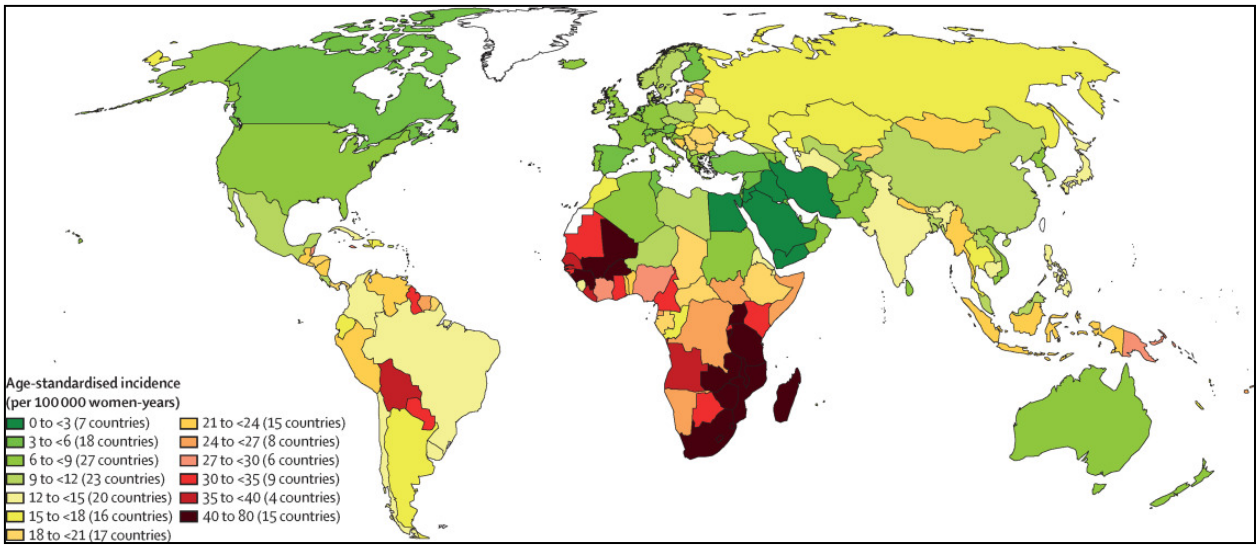

Fig 1.2: Geographical distribution of world age-standardised incidence of cervical cancer by country, estimated for 2018.
Source: https://www.thelancet.com/journals/langlo/article/PIIS2214-109X(19)30482-6

HPV (Human papilloma virus) is a virus which causes infection of human reproductive tract. In most of cases, cervical cancer occurs mainly due to infection of HPV which is sexually transmitted. Precancerous lesions may take place due to persistent infection with specific types of HPV. Untreated precancerous lesions can give rise to cervical cancer. There are several risk factors such as smoking, contraceptive pills, sexual intercourse at young age, weak immune system and multiple sexual partners (Dunne and Park, 2013). About 90% of cervical cancer cases are squamous cell carcinomas, 10% are adenocarcinoma, and a small number are other types (*World Cancer Report 2014*. W.H.O).

1.2. Therapeutics of Cancer:

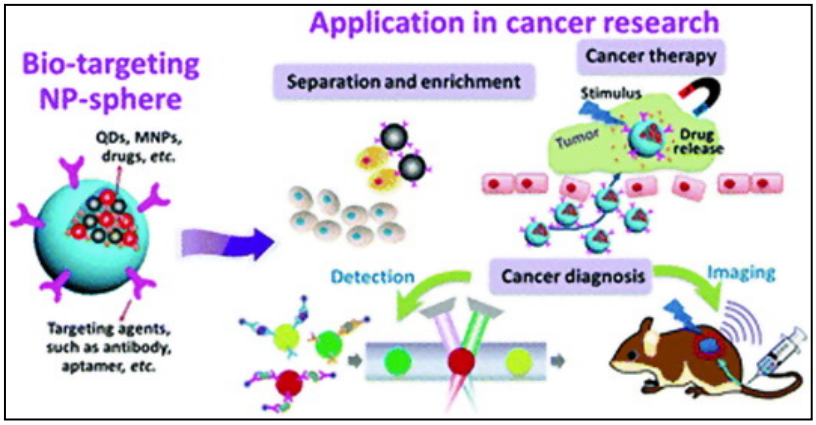

Fig 1.3: Different application of nanoparticles in cancer research. **Source**: https://doi.org/10.1039/C5NR08534A

Several different treatment techniques have been developed to combat cancers and that have been categorized into five groups: chemotherapy, surgery, radiation, targeted and immunotherapy (Feng and Chien, 2003). The selection of a treatment technique is based upon several factors, like the location of the tumor, grade and stage of the tumor, patient's condition all have to take under consideration before the treatment. The conventional cancer treatment comprises with three basic methods: operations, chemotherapy and radiotherapy. Although immunotherapy and hormone therapy are there but the use of these therapies is limited. Application of immune therapy is mainly executed in research but very less in the practice field of therapy. But the hormone therapy is applicable in breast cancer treatment.

At present therapeutic drugs such as Methotrexate (MTX) (Cudmore et al., 2014), 5-FU (Yim et al., 2004), capecitabine, cisplatin (Wang et al., 2016), gemcitabine, Paclitaxel, doxorubicin (Cortés-Funes and Coronado, 2007; Thorn et al., 2011) and Tamoxifen (Ferrandina et al., 2001) are used for the treatment of breast and cervical cancers. But due to the toxic effects of these drugs, adverse effects such as cytopenia, liver damage (Sharma et al., 2014), mucocutaneous problems, alopecia (Rossi et al., 2017), allergic interstitial pneumonitis, cardiotoxicity (Altena et al., 2009), adverse neurological effects (Stone and DeAngelis, 2016) etc. was observed.

1.3. Role of Nanoparticles in cancer therapy:

Metallic nanoparticles have captivated researchers for over a century in the application of biomedical sciences and engineering. Nano materials can be prepared and modified using chemical functional groups, which facilitates in binding with appropriate antibodies, ligands and drugs. Conjugated nano materials open a new avenue in applications of magnetic separation, preconcentration of target analytes, vehicles for gene and drug delivery, targeted drug delivery,

and more importantly in medical imaging. Nanotechnology is the division of science and engineering, which deals with materials of sizes 100nm or less (Salata, OV. 2004). There are several types of metal oxide nanoparticles such as ZnO, CuO, TiO2, MgO, NiO, ZrO2 nanoparticles etc (Noguera, C.1996; Kung, HH. 1989). Unique physico-chemical properties of Metal oxide nanoparticles are related to low surface energy, high density of NPs and restricted size of edge on the surface sites. Due to these interesting properties nano materials become more stable than bulk materials.

Among several metal oxide nanoparticles copper oxide (CuO) nanoparticles have drawn the attention due to their good antimicrobial and biocide properties (Wang et al., 2017, Perreault et al., 2012). Copper oxide has been used in several applications such as such the development of supercapacitors, near-infrared filters, in magnetic storage media, sensors, catalysis, semiconductors, etc. (Jo et al., 2015, Devi et al., 2014, Dagher et al., 2014). Among various plants, *Azadirachta indica* (*A. indica)*, a traditional medicinal plant which grows mainly in tropical and semi-tropical climates has been found to have versatile applications in medical science (Puri, HS. 1999). The leaves, flowers, fruits and seeds of *A. indica* have promising chemopreventive and therapeutic properties (Morgan, ED. 2009). In addition, *A. indica* extracts have shown selective cytotoxicity towards cancer cells as compared to normal cells, thus being significant in reducing toxicity during cancer therapy (Hao et al., 2014).

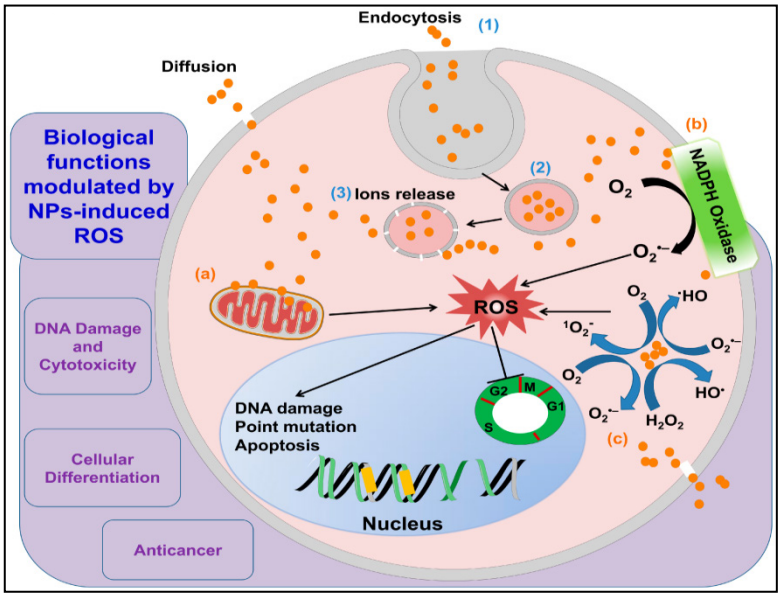

Fig 1.4: schematic diagram describing the mechanisms implicated in NP-induced ROS production. NPs can be internalized into the cell by (1) endocytosis; (2) formation of the endocytotic vesicles; and (3) release of particle ions from vesicles into the cell.
Source: https://doi.org/10.3390/ijms18010120

Through disruption of cell cycle progression, *A. indica* extracts suppress the proliferation and growth of tumor cells. Pertaining to previous reports, neem seed oil inhibits the growth of Hela cervical cancer cells (Ricci et al., 2008).

A targeted system relying on nanocapsules, nanoparticles, nanofibers, nanocrystals, nanorods, liposomes, pH-sensitive liposomes, temperature-sensitive liposomes, etc. facilitates therapeutic drugs to reach the specific site in the cell and the overexpressed receptors of cancer cell surface also facilitate the process.

For the targeting of cancer cells, some points should be considered to get better efficacy of candidate drugs with the help of nanotechnology-based materials. Cancer cells possess leaky vasculature, high hydrostatic pressure, and presence of over-expressed receptors, angiogenesis and EPR effect. Cancer cells require more nutrition as a fuel for their growth. On the other hand particle size, surface charge, hydrophilicity, hydrophobicity and covalent attachment with the ligands are specific for overexpressed receptors. Intracellular excess ROS generation can destroy the balance and simultaneously encourage cancer cell cycle arrest, senescence and apoptosis. Apoptosis is attributed to mitochondrial oxidative stress. Due to oxidative stress mitochondrial membrane potential reduces and increases cytochrome C releases in the cytosol which activates cascade of Caspases and ultimately leads to cell death (Cadenas and Davies, 2000; Simon et al., 2000). Additionally, superoxide generation through the Rac-1/NADPH oxidase pathway can utilize proapoptotic signaling (Chung et al., 2009).

Nanoparticles are a prime candidate for cancer immunotherapy. Nanoparticles with their interesting characters such as size, shape, charge, elasticity and ability to work as a carrier are able to act as a platform for immunotherapy (Goldberg, MS. 2015; Fan and Moon, 2015). Especially inorganic nanoparticles have achieved several successful steps towards cancer immunotherapy. The bioactive nanosystem has several advantages like high targeting efficacy, less toxicity, biocompatibility and high specificity, though the costing for immunotherapy is very high in clinical perspective. Surgery, chemotherapy, radiotherapy, hormone therapy, and immunotherapy are the different ways to treat cancer though, not without several side effects. Side effects are the main drawbacks of these current treatments (Kokate, R. 2017). Among the several treatment methods employed, immunotherapy for cancer is very effective because of its ability to boost the natural defense mechanism against cancer (Farkona et al., 2016).

Manipulation of the immune system has been considered as a breakthrough phenomenon in cancer immunotherapy. Manipulation of immunotherapy can be done at the molecular and cellular levels (Neves and Kwok, 2015; McCune, JS. 2018; Sun, W. 2017). The tumor immune response consists of several complex events and still now very little are familiar to us. Several studies have showed the attention-grabbing mechanisms related to innate and adaptive immunity which helps to maintain the equilibrium in our system are responsible behind the immune response (Dougan and Dranoff, 2009; Spranger and Gajewski, 2018; Pandolfi et al., 2011). The conventional method of cancer treatment has been improved by the use of nanoparticles as an antigen and adjuvant delivery vehicle for a better result (Zang et al., 2017).

Nanocarriers are able to increase the intracellular concentration of drugs in cancer cells by active and passive targeting. Targeted nanocarriers elicit anticancer effects and reduce cellular and system toxicity (Chen et al., 2011). Noninvasive strategies for cancer therapy were not possible before the implication of nanotechnology-based therapy. In this regard engineered nanoparticle drives the technology towards a new path. The surface chemistry of NPs affects the cancer cells by the interaction with the surrounding environment. Functionalized NPs play a crucial role in targeted anticancer therapy.