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Biomarker Related to Early Detection of Lung and Breast Cancer.

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ABSTRACT.
Cancer causes the largest number of deaths in the world accounting for 10 million deaths in 2020. Out of the many cancers plaguing us, breast cancer tops the list with 2.26 million cases and 685,000 deaths followed by lung cancer having 2.21 million cases and 1.80 million deaths recorded in 2020. However if lung cancer is diagnosed in its premature stages (stages I-II), five year survival rate comes around 56 percent. Inspite of enhanced imaging detection and tissue biopsy breast cancer detection remains poor leading to ineffective treatment. Moreover, the common metastatic site for breast carcinomas is in the lungs. Patients who lived longer than 10 years after breast cancer showed 40 percent increased risk of occurrence of lung cancers. Circulating tumour biomarkers like circulating tumour cells (CTCs) ,cell-free DNA (cfDNA),circulating tumour DNA (ctDNA),microRNA and exosomes provide non-invasive methods for early diagnosis of lung and breast neoplasms. Circulating biomarkers gives us idea about actionable mutations and tumour characteristics. They can be collected at higher frequencies than imaging or tissue sampling and thus give us better results.
Key Words: Breast neoplasm; circulating tumour cells; cell-free DNA; exosomes; mutations.(Source: MeSH-NLM).

I. INTRODUCTION.

Biomarker or biological markers are certain signs that indicate the medical state of the patient non- invasively , accurately and reproducibly.[1] Cancer biomarkers are those that segregate a cancer affected patient from an non-diseased person. The differences can be due germ line or somatic mutations, transcriptional changes and post translational modifications.It can be any biological molecule in blood, other body fluids, or tissues.It can also be present in excretions or secretions like stool, urine, sputum.Biomarkers can be alternations in gene expression, proteonomic or metabolic signs.[2]

Female Breast Carcinomas are most common with 2,261,419 new cases and 684,996 deaths in 2020. It is followed by lung carcinomas with 2,206,771 new cases and 1,796,144 deaths in 2020.[3] 1.9 million new cancers cases and 609,360 deaths from cancer are expected to occur in U.S in 2022. Lung cancer continues to cause more than 350 deaths each day, which is greatest number for all types of cancer. 81% of fatalities from lung carcinomas are caused from smoking cigarettes. Second to smoking, the next greatest lung cancer cause is radon gas exposure released from soil.[4]

Estimates predict that 287,850 women in U.S would be diagnosed with invasive breast cancer and 51,400 women would get in situ breast cancer. The average 5-year survival rate for women in U.S with non- metastatic invasive breast cancer is 84%. The 5-year survival rate for women with invasive breast cancer is 99% if it is limited to the breast. This stage of breast cancer is detected in 65 percent of female patients. Women between the ages of 15 and 39 in the United States have a lower likelihood of receiving an early breast cancer diagnosis (47% of cases in this age group) than do women over the age of 65 (68% of cases in this age group). This may be the case since, unless a person is at a greater risk, most breast cancer screening programmes do not start until age 40. The chance of survival for five years is 86% if the cancer has progressed to nearby lymph nodes. The 5-year survival rate is 29% if the cancer has progressed to a distant area of the body. Black women have a 10% lower breast cancer survival rate than White women have. When a woman is initially diagnosed with breast cancer, 6% of them have cancer that has progressed beyond the breast and local lymph nodes. "De novo" metastatic breast cancer is the term used for this. New medicines allow many breast cancer patients have a good quality of life for a while even if the cancer is discovered at a

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more advanced stage.[5]

It is well known that environmental agents including occupational dangers can affect cancer causation along with genetic and lifestyle-related factors.Evidence suggests that prevention of occupational and other environmental hazards linked to cancers reduces incidence as well as mortality in an economical manner. Since breast and lung cancers are so prevalent in the society, eliminating hazards is a great public health strategy.[6] Both active and passive smoking is the leading cause of lung cancer in the world. Almost 76% of adults started smoking before 18. As high as 5700 kids start vaping every day. Thus prevention of smoking habits remains a public health challenge. Increasing air pollution due to industries and vehicles are also contributing to lung cancer among people.[7] Public health research promotes development of portable, and low cost cancer screening and diagnosis in a local care setting. Since 1973, the Surveillance, Epidemiology and End Results (SEER) programme of the National Cancer Institute has gathered and published reliable data on the incidence, mortality, and survival trends of many cancer types. Understanding these trends has aided in concentrating research initiatives and governmental initiatives. A further reduction in cancer risk, incidence, and mortality as well as improvements in the lives of cancer survivors and the general population will be achieved with additional investments in cancer control, population health, and survivorship research.[8] This study aims to extensively review possible biomarker for lung and breast cancer for their early detection.

II. METHODS

Search Strategy

This is a narrative review. We searched scientific materials using PubMed and Google Scholar. Various Key words like ‘ Biomarkers’, “ cell free DNA”,”cancer biomarkers”,“Circulating tumour cells”,”public heath impact of breast cancer” were used in the above mentioned search engines. We used “Or” and “and” operators during literature search. Relevant articles were included after conducting a second search of the references of the chosen articles.

Selection Criteria

Papers not discussing lung cancer or breast cancer were excluded from study after screening titles, abstract and full text reading. Only articles in English were included. Articles including the terms like “biomarkers” or “exosomes” or ” tumour markers” were included.

III. RESULTS.

A total of 12 papers were included in this review. This review included 7 articles and 5 websites covering mainly the American population but cases of Indian and African American origin were also included.

Tumour derived cell-free DNA (cfDNA) is a cost effective and efficient biomarker for cancer detection .It can detect point mutations related to cancer, copy number variations and methylation markers at quite an early stages of disease.[9] Cell-free Dna is a double stranded nucleic acid with lower molecular weight than genomic DNA circulating in blood and tissue fluids. Necrotic cell release cf-DNA with higher molecular weight than normal apoptotic cells. This property is used to estimation of tumour-derived portion of cf-DNA. The fraction of cell free DNA that contain tumour specific alternations is named as Cell- free circulating tumour DNA (Ct-DNA).CtDNA gives information about the size stage and lymph node involvement in breast cancer.[10] Cf-DNA is also elevated in patients of COPD and lung cancer.Cell injury due smoking contributed to higher apoptosis of cell leading to higher Cf-DNA.[11] Cf-RNA also used for cancer detection but not used widely as RNA is unstable and also due to presence of RNAases in plasma and body fluids. Cf-RNA also gives false positive frequently.[10]

Exosomes are 30–150 nm endocytic membrane vesicles that are released by various cell types into the extracellular space**,** including body fluids such as blood, lymph, cerebrospinal fluid, urine**,** and saliva. These extracellular vesicles are functional vesicles that carry a complex cargo of nucleic acids, proteins and enzymes, depending on the nature and state of the cell of origin.

Exosome biogenesis begins within the endosomal system where early endosomes mature into late endosomes (MVBs), and inward budding of the endosomal membrane creates an accumulation of intraluminal vesicles (ILVs) in the lumen of the organelle.During this process, transmembrane proteins are integrated into the invaginated membrane and cytoplasmic components are trapped within the ILV. The

endosomal sorting complex (ESCRT) required for trafficking is a protein machinery composed of sequential complexes (ESCRT-0, -I, -II, and -III) associated with the membrane of the MVB. All components coordinately control vesicle budding and protein charge sorting in a ubiquitination-dependent manner. The ESCRT mechanism begins with ESCRT-0, which recognizes and sequesters ubiquitinated proteins in late endosomal membranes. After the initial retraction of the restrictive membrane into her MVB lumen caused by ESCRT-I/II, ESCRT-III facilitates the budding process and divides the buds into her ILVs. Therefore, ATPase Vps4 facilitates cleavage of the ESCRT-III complex from the MVB membrane. Sorting of proteins within the ILV can also occur independently of ubiquitination. Recent studies have revealed a new mechanism involving syntenins and syndecans . Moreover, various lines of evidence point to an ESCRT-independent mechanism of exosome biogenesis involving exosomal lipids. After maturation, MVBs can fuse with the plasma membrane and release trapped ILVs called 'exosomes' into the extracellular space. Alternatively, these vesicles are trafficked to lysosomes and their cargo is depleted.[11] The mechanism of exosome biogenesis appears to be deregulated in cancer, leading to increased amounts of vesicles released from cancer cell lines and found in the blood of cancer patients. Notably, in breast cancer, the release of exosomes from the human tumor cell line B42 clone 16 was shown to be significantly higher compared to the amount of exosomes released from his HMEC B42, the parental normal mammary epithelial cells. Furthermore, in vitro studies highlight increased release of exosomes in cells maintained under cellular stress conditions such as hypoxia , suggesting that exosome secretion is mediated by the Ca2+/Ca2+-dependent Rab binding protein (Munc13-4) pathway. shown to be [twenty three]. We recently showed that the adipokine leptin may be another important inducer of exosome release in breast cancer. Indeed, the leptin/leptin receptor axis, which regulates the expression of heat shock protein 90, a leptin target gene, inhibits protein expression of tumor susceptibility gene 101 (Tsg101), a key component of the ESCRT-I complex. I understand. This mechanism leads to increased MVB formation and exosome secretion in both estrogen receptor-positive MCF-7 and triple-negative MDA-MB-231 breast cancer cells .

CA125 is proposed as a serum biomarker for ovarian cancer, but elevated levels have been observed in up to 84% of metastatic breast patients, and correlated with the metastasis-associated burden in pancreatic cancer . CA15-3 is routinely used in monitoring therapy and predicting recurrences in patients affected by breast cancer. The serum levels of CEA, CA125 and CA15-3 were demonstrated to be of great value in the management of patients with breast cancer, and could serve as predictive indicators and for monitoring the course of disease.[12]

IV. DISCUSSION.

From the above results it is evident that non invasive tumour markers like cfDNA , exosomes and CA-125 provide useful information for early diagnosis of breast and ovarian cancer. cfDNA is most cost effective and can be tested for in moderately equipped laboratories and clinic thus improving the reach of testing. Exosomes are also an important biomarker for breast cancers but unlike cfDNA it does not provide information about the size and lymph node involvement in cancer.CA-125 is the most common biomarker for cancer.It is mainly used for ovarian cancer but it is seen that almost 84% of breast metastasis cases have been positive for CA-125 test and thus providing information of secondary breast carcinomas.

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