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Decisive tools of breast cancer: Advances in technologies

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Short communication

Worldwide life-threatening breast cancer is about 23% and known to be the second largest number of deaths among all cancers. Breast cancer incidence is varied among different ethnic groups and said to be more common in White females than in Asian or Black females. It is evident that genetically inherited mutations and alterations in BRCA-1 and BRCAS-2 genes would enhance the risk of developing breast cancer. Most invasive malignant breast tumors with a disproportionate increase are most commonly occurring in the upper-outer quadrant of the breast [1]. It is unbelievable to think, but mounting evidences from research supports the involvement of endogenous estrogen as a carcinogen among breast cancer patients [2].

Such of those women who begin menstruating early or even start menopause late naturally produce more estrogen during their lifetimes leading to higher risk of breast cancer by stimulating tumors. Of several types, hormone-sensitive breast cancer is elicited by two different principle hormones estrogen (ER) and progesterone (PR) [3]. These endogenous hormones will bind to their specific receptor proteins to signalize cells to grow and multiply. HER2 is a protein receptor resembles the human epidermal growth factor receptor . HER2 protein amplification or over-expression from its oncogene has been shown to play an important role in the development and progression of breast cancer. Recently, the protein has become an important biomarker and target of therapy for over 30% of breast cancer patients.

In recent days, a combination of breast imaging for screening and diagnosing cancer is becoming critical and indispensable [4]. Breast imaging is being preferred as an adjunct to mammography. The digital mammography is proven and has become medically necessary for patients with dense breast tissue. Breast magnetic resonance imaging (MRI) is also proven and medically necessary for patients at high risk for breast cancer to help in identifying cysts and fluid-filled sacs to determine the possibility of higher risk of breast cancer.

A biopsy from the suspected tumor regions will show the presence of such receptor proteins. If the cells of a tumor are having receptors for estrogen then the tumor is said to be ER-positive and similarly for progesterone, PR-positive. It is evident from the tests that 2 out of 3 breast cancers are hormone sensitive [5]. A biopsy sample of the breast tumors tested for HER2 is crucial and the followings methods have become the needs of the day:

i. Immunohistochemical stains (IHC), where special markers are used to identify the HER2 protein [6]. In the presence of many copies of HER2 color intensity will be more than the normal and is visualized under a microscope.

ii. As the HER2/neu gene makes the HER2 protein, fluorescent in situ hybridization (FISH) will become more useful method. In fluorescent in situ hybridization, the fluorescent pieces of DNA will stick to the copies of the HER2/neu gene inside the cells, which can then be counted under a special microscope [7,8].

iii. More recently, a newer type of cost-effective test being adopted called "chromogenic in situ hybridization (CISH)", much similar to FISH, where by using small DNA probes to count the number of HER2/neu genes and thereby HER2 protein in breast cancer cells [9]. As the test is based on the change in color intensity (not fluorescence) require no special microscope and analysed by a colorimeter. In the case of HER2-negative breast tumors, the determination for either HER2 genes or their proteins becomes insignificant. Triple-negative breast tumor cells neither possess too much HER2 nor even estrogen or progesterone hormones binding receptors. Such breast tumor cells designated as HER2-, ER-, and PR-negative, respectively.

Recently, the area of 'Precision Medicine' is unparalleled and trying to understand the biology of the disease and providing molecular information to tailor the drug therapy of patients. Emphasis is being laid on the massively parallel sequencing of single cells [10] and minimally invasive approaches in order to characterize cancer mutations in blood [11]. Breast cancer tumor progression is associated with numerous genetic and epigenetic alterations, most of which can also be detected as cell-free nucleic acids (cfNAs) in plasma and serum. The cfNAs might be excellent blood cancer biomarkers, as they may be more informative, specific and accurate than protein biomarkers. In breast cancer patients, tumor cells release circulating DNA, mRNA, and microRNA into the blood circulation reflecting the characteristics of the primary tumor and even of micro-metastatic cells, as excellent blood biomarkers. Changes in the levels of circulating nucleic acids have been associated with tumour burden and malignant progression.

Today, specific focus on the clinical utility of cell-free nucleic acids as blood biomarkers and ctDNA as a liquid biopsy has enormous potential and promising area of investigations for both researchers and clinicians. The analysis of ctDNA is challenging because the tumor contribution to cell-free DNA is diluted in the background of normal cell-free DNA. The development of massively parallel sequencing and digital genomic technologies has allowed both screening and validation of genomic alterations. Rigorous studies on genomic characterization of 'liquid biopsies' in breast cancers will need robust assays for analytical validity to demonstrate clinical validity and to become available at the clinical settings. For the last one decade, advances in massively parallel

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sequencing technologies have enabled the genomic characterization of driver genes and actionable mutations in breast tumour [12]. Any deviation in tumour-derived somatic single nucleotide variants (SNVs) or copy number alterations (CNA) and even structural variants (SVs) can be detected in ctDNA from breast cancer patients [13]. These highly sensitive techniques include normal PCR and digital PCR-based tools [14] in addition to sequencing facility [15].

The article emphasizes on the advancement of revolutionizing nanotechnology, which has changed the very foundations of cancer diagnosis, treatment, and prevention involving novel nano-devices and biosensors [16]. Nanotechnology offers a novel set of tools for rapid detection and diagnosis, site targeted drug delivery by allowing for multiparametric analysis using relatively small sample volumes and biomarker research in cancer [17]. Mainly, four specific nanotechnology applications that could impact on biomarker research for early detection are as follows: (a) nanostructures such as pores, (b) nanoprobes such as scanning tunnel microscopy, (c) nanosources such as laser-induced fluorescence, and (d) nanomaterials such as superparamagnetics and quantum dots [18].

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