

A REVIEW ON SCREENING METHODS OF BREAST CANCER, CANCER BIOMARKERS AND PHYTOCONSTITUENTS AGAINST BREAST CANCER

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ABSTRACT

A cancer biomarker refers to a substance or process that is used as an indicative the presence of cancer in the body. A biomarker may be a molecule secreted by a tumor or a specific response of the body to the presence of cancer. Biomarkers are utilized in three elementary ways as a diagnostic tool, prognostic tool, and predictive tool. The screening tests employed are clinical and breast exams, mammography, hereditary screening, ultrasound, and attractive reverberation imaging. Biomarkers involved in breast cancer are human epidermal growth factor-2, estrogen receptor, progesterone receptor, Cyclin D1, and Cyclin E. Specific bioactive phytoconstituents used as anticancer include curcumin, genistein, resveratrol, isothiocyanates, silymarin, diallyl sulfoxazole, lycopene, apigenin, and gingerol. Hence, this review indicates the study of screening methods, various biomarkers in breast cancer and phytoconstituents against breast cancer.

Keywords: Cancer biomarker, Breast cancer, Phytoconstituents, Screening methods.

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INTRODUCTION

Breast cancer is considered to be one of the common cancer-related cause of death among females. Among women, it caused a major public health concern nearly 1 in 3 cancers diagnosed. It is one of the life-threatening diseases in a woman and they have to face during her lifetime. An increasing incidence of breast cancer reported over the past few decades and leads to the development of new anticancer drugs particularly from plants which showed a large amount of scientific evidence in lowering the risk of cancer [1].

Western European rates five-fold greater than Eastern/Middle Africa toward the incidence of breast cancer. The mortality rates also get differ in Southern/Western African which rates 3 times those of Eastern Asia [2]. By reductions in case fatality, higher incidence in developed countries largely attributable to mammographic screening and also there will be improved adjuvant therapy [3]. To manage the disease, it requires integration of clinical, pathological and biological parameters [4]. The risk stratification was considered to be prognostic histopathological variables which include tumor size, tumor grade, and lymph node status. Such individual prognostic parameters have been developed into the tumor, node and metastasis staging system [5] and Nottingham prognostic index [6,7]. In addition to this, various biomarkers (immunohistochemical markers) such as estrogen receptor alpha (ER α), progesterone receptor (PR), and the human epidermal growth factor receptor 2 (HER2) also represent mandatory elements for treatment [8,9].

The biomarker-based treatment implements learning points for lower resource settings. First, it involves successful delivery mandates technical and analytical consistency, as incorrect profiling of basic parameters is profoundly detrimental. This has been governed by authoritative guidance from the American Society of Clinical Oncology (ASCO) and College of American Pathologists [8,9] and quality assurance by the United Kingdom National External Quality Assessment Service [10]. Second, despite novel biomarkers, indices and signatures, few have clinical utility. So according to this, guidance for reporting of tumor marker studies [11] and a tumor marker utility grading system (ASCO) has been published [12,13]. Third, the international availability of biomarkers remains very uneven and confounded by inferences

from developed health-care systems than specific evaluation in lower resource settings. BRCA1 is the leading mutation leading to breast cancer [14].

Determining the ER, PR, and HER2/neu receptor status in breast cancer becomes medical practice nowadays. Clinical trials have shown the survival advantage for patients with hormone receptor positive status by treatment with adjuvant hormonal or chemotherapeutic regimens [15].

In normal cells, this gene is involved in DNA repair, transcription regulation, and tumor suppression. To prevent cancer, it has been studied that diets rich in phytochemicals can reduce the risk of cancer by 20%. Plant natural product (phytoconstituent) has played an active role in generating a significant number of drug compounds in drug discovery program. Secondary metabolites and their derivatives from plants and other natural resources have been used for the treatment of various diseases [16].

In this review, established and emerging biomarkers, screening methods and various phytoconstituents were considered with reference to biological significance, clinical utility and resource implications.

CANCER BIOMARKER

"A cancer biomarker refers to a substance or process that is indicative of the presence of cancer in the body. A biomarker may be a molecule secreted by a tumor or a specific response of the body to the presence of cancer. It might be used to view how great that body response on medicine for an infection alternately condition. In addition, it is also called as an atomic marker [17]." Biomarkers about malignant might incorporate an expansive range from claiming biochemical entities, for example, nucleic acids, proteins, sugars, lipids, also little metabolites, cytogenetic also cytokinetic parameters and also entire malignant units discovered in the body liquid. A thorough understanding of the significance of every biomarker will be a chance to extremely critical not best for diagnosing the ailment reliably, as well as help in the decision of different restorative plan at present accessible that is liable will profit the patients [18]. Biomarkers are utilized within three elementary ways as a diagnostic tool, prognostic tool, and predictive tool [19].

Predictive carcinogenic biomarkers involve mutations in genes such as KRAS, p53, epidermal growth factor receptor, erbB2 for colorectal, liver, and pancreatic cancer; mutations in genes such as BRCA1, BRCA2 in breast, and ovarian cancer; abnormal methylation for malignant genes p16, CDKN2B, and p14ARF for forebrain cancer; hypermethylation for MYOD1, CDH1, and also CDH13 in cervical cancer; also hypermethylation of p16, p14, and RB1 for oral carcinoma [20].

Other illustrations of biomarkers [21]:

- Carcinogenic suppressors lost over malignancy. Examples: BRCA1 and BRCA2
- RNA. Examples: mRNA and microRNA
- Proteins found previously, figure liquids or tissue. Examples: Prostate-specific antigen, furthermore CA-125.

SCREENING METHODS

Breast malignancy screening will be the restorative screening for asymptomatic, clearly solid ladies to breast malignancy previously, an endeavor to accomplish a sooner analysis. The supposition is that initial identification will enhance results. An amount for screening tests have been employed, including clinical and breast exams, mammography, hereditary screening, ultrasound, and furthermore attractive reverberation imaging [22].

Mammogram

A mammogram will be the proposed system for breast malignancy screening for those normal hazard populace. It will be that main screening modality demonstrated to decrease breast malignancy mortal sin. Time permits dangers to incorporate false negative outcomes also a false sense of security that might delay diagnosis; additional tests also tension connected with false sure comes about; and the truth that breast malignancy might be diagnosed for no change in the length or personal satisfaction about existence [23]. Higher the breast thickness will be connected with higher bosom disease danger previously, both premenopausal what's more postmenopausal ladies [24]. On the other hand, ladies for greatly low densities need to be as of late indicated to hold a fundamentally more awful prognosis regardless of patients' age, body mass index what's more menopausal status [25]. Breast malignancy was troublesome and it should be identified through mammograms did ladies for secondary breast thickness in light of practical malignancy thick breast tissues bring a comparable presence ahead of the mammillary body. Likewise a result, higher breast thickness is connected with a higher rate of false negatives (missed cancers) [26].

Atomic breast imaging

Atomic breast imaging is an atomic pharmaceutical system that is at present under investigation. It demonstrates guaranteeing effects for imaging skin for thick breast tissue furthermore might have accuracies tantamount to magnetic resonance imaging (MRI). It might be superior to a mammogram to some people with thick breast tissue, identifying 2 to 3 times more growth in this populace [27]. It, in any case, carries a more excellent danger about radiation harm making it improper to general breast malignancy screening [28]. It will be conceivable to decrease the measurement from claiming radiation utilized [29].

Ultrasonography

Therapeutic ultrasonic will be asymptomatic help with a mammogram. Including ultrasonic trying to ladies for thick breast tissue expands that identification from claiming breast cancer, as well as expands false [30]. There will be insufflated proof to help the utilization about ultrasonography to schedule screening in the normal danger populace. Ultrasonography ought not to be utilized likewise a solitary screening test. It might need a part likewise an assistant with mammogram previously, screening ladies for thick breasts, concerning illustration resolved toward a radiologist. Ultrasonography aides should recognize small, mammographically mysterious cancers; however, those generally sure predictive worth from claiming screening ultimo callous may be low.

Magnetic resonance imaging

Attractive reverberation imaging (MRI) need to be indicated will recognize growths not unmistakable ahead mammograms. Those Head quality for breast MRI may be its high negative predictive worth. A negative MRI could discount the vicinity of malignancy, and it will be a second degree for certainty, making it a phenomenal device around for screening in patients toward secondary hereditary danger alternately radiographically thick breasts, in pre-treatment arranging the place the degree of malady may be troublesome will determine through a mammogram. MRI might diagnose consider proliferative change, fibroadenomas, different normal discoveries in a glance, frequently eliminating those require to unreasonability and unnecessary biopsies alternately surgical methods. The spatial transient determination for breast MRI needs to be expanded for later years, making it could be allowed with recognizing alternately discount that vicinity for little *in situ* cancers, including ductal carcinoma *in situ* [31].

Signs for utilizing MRI to screening include solid family history about breast malignancy, patients with BRCA-1 alternately BRCA-2 oncogene mutations, assessment from claiming ladies for breast implants, historical backdrop from claiming past lumpectomy alternately breast biopsy surgeries, axillary metastasis for an obscure elementary carcinogenic, and exceptionally thick alternately scarred breast tissue [32]. MRI ought further bolstering not be utilized to screening the normal hazard populace. MRI might be utilized within particular condition likewise dictated toward a radiologist.

BRCA ANALYSIS

BRCA1 and BRCA2 mutations are the pre-eminent common cause of hereditary breast disease [33]. It was considered as human genes that produce tumor suppressor proteins, and it helps in repairing damaged DNA and play a role in ensuring the stability of the cell's genetic material. BRCA 1 and BRCA 2 mutations cause 20-25% of hereditary breast cancer [34] and 5-10% of all breast cancers [35] and specific inherited mutations of these gene increases the risk of female breast and ovarian cancers, and they have been associated with increased risks of several additional types of cancer [36].

BIOMARKER IN BREAST CANCER

Human epidermal growth factor-2

HER-2 may be a paramount gene to subatomic focusing on medicine for breast malignant [37]. Determination of ER status about obtrusive breast carcinoma may be suitable as a prognostic and predictive figure, and ER+ predicts for a light of endocrine help for example, such that antiestrogen (tamoxifen) organization alternately ovarian concealment. Similarly, mankind's epidermal development component receptor 2 (HER2) positivity is handy for selecting focused on treatment with monoclonal immune response (trastuzumab) against HER2. Recently, microarray profiling from claiming obtrusive breast carcinoma need distinguished five different subtypes from claiming morphologically comparative breast malignancy (luminal A, luminal B, typical breast-like, HER2-overexpressing, furthermore the basal-like subtype), representing something like 15% for breast malignant situations furthermore portrayed toward cynicism for ER, PR, furthermore HER2, is connected with combative histology, poor prognosis, What's more lethargy of the ordinary endocrine therapies, shorter survival, and BRCA1-related breast malignancy [38,39]. Exactly breast malignancy needs a shelter amount for HER2 receptors. The additional HER2 receptors animate those malignancy units will separate What's more developed. When there would be higher levels of the HER2 protein done a breast cancer, it is known as HER2 certain breast malignant. The HER2/erbB2 gene, cell surface receptor tyrosine kinase is a pro-oncogene for signal transduction in cell development and division [40,41].

Estrogens receptor

Estrogens assume a huge part clinched alongside directing those development separation about normal, premalignant, harmful types, particularly breast epithelial cells, through interactional with

two atomic ER (ER α or ER β) [42]. The ER is a capable predictive and prognostic marker, as well as a productive target to that medication from claiming hormone-dependent breast tumor for antiestrogens [43]. Estrogen impacts would exert through two sorts for particular receptor: ER α and ER β [44]. These atomic receptors would ligand-dependent interpretation elements that intercede those living impacts about estrogens and antiestrogens. Estrogen, 17 β -estradiol (E2), assumes a noticeable part to mediating the maturation, proliferation, differentiation, apoptosis, inflammation, metabolism, homeostasis, and impacts the growth and improvement about breast malignant. ERs act principally toward directing the outflow for target genes whose promoters hold numerous particular successions called estrogen-responsive component [45].

Progesterone receptor

Progesterone will be an intense breast mitogen. An essential capacity from claiming progesterone/PR will be should intercede the monstrous development of epithelial-derived mammary alveoli (amelogenesis association for alveoli under lobules) throughout puberty and pregnancy on preparation to lactation. PRs are ligand-activated interpretation element parts of the steroid hormone receptor (SR) subfamily. PRs capacity not just as basic controllers about interpretation as well as on initiate indicator transduction pathways, a number about which are included for pro-proliferative indicating in the breast [46-48].

Cyclin D1

Cyclin D1 is a right on time light of mitogenic incitement to a few cell types, yet the outcomes of the modified statement of this gene clinched alongside mankind's units about epithelial root stay undefined. We access the impacts for alterations for Cyclin D1 outflow in human breast malignant phones by generating T-47D units expressing mankind's Cyclin D1 under the control of a zinc-responsive metallothionein promoter [49]. The division also answers from claiming eukaryotic phones are intercede toward an arrangement of facilitated occasions that create a "cell cycle collins [50]." The cycle comprises a mitotic stage (M phase) an interim between succeeding mitoses (interphase). The M period is made from claiming both mitosis and cytokinesis. There are two fundamental aggregations for the cycle: G1/S cyclin that intercedes G1/S transition including Cyclin A, Cyclin D, and Cyclin E; and G2/M cyclin that controls progression from G2 to M phase, for example, Cyclin B [51]. D-type cyclins cooperation with CDK4 and CDK6 over promptly will work G1 phase, same time cycling prefers should CDK2 to late G1 phase [52]. Three D-type cyclins named Cyclin D1, D2, and D3, constantly on for which need aid prompted toward mitogens. Withdrawal the mitogens throughout G1 period makes fast debasement of D-type cyclin.

Cyclin E

Cyclin E will be a critical controller about cell cycle progression that together with the cyclin-dependent kinase (CDK) 2 may be vital for the G1, S move throughout those mammalian cell cycle [53,54]. It is a 50-kD cycle protein, as well as up to five low-molecular-weight isoforms of cyclin. These isoforms, which need that aminic terminus, would hyperactive, concerning illustration compared with that full-length protein, in phosphorylating substrates prompting progression starting with that G1 stage of the S period. Cyclin and their reactant CDK accomplices act positively to propel a cell through those proliferative cycle [55,56]. Actuation from claiming cyclin-CDK complexes brings about a course of protein phosphorylation that eventually actuate cell cycle progression.

PHYTOCONSTITUENTS AGAINST BREAST CANCER

- Characteristic plants have been used to prevent also will treat different illnesses for many a considerable length of time [57]. There are phenomenal wellsprings of bioactive segments exerting their wellbeing valuable effects, furthermore often, these wellsprings are materials for gourmet nourishment utilizations. Specific bioactive segments starting with the plants need to be affirmed to their

anticancer exercises [58]. These incorporate curcumin starting with turmeric, genistein starting with soybean, tea pack polyphenols starting with green tea, resveratrol from grapes, sulforaphane starting with broccoli, isothiocyanates from cruciferous vegetables, silymarin from milk thistle, diallyl sulfisoxazole from garlic, lycopene starting with tomato, rosmarinine corrosive starting with rosemary, apigenin starting with parsley, and also gingerol from gingers [59].

- Apigenin, a flavone present in parsley, celery, chamomile [60] and Egyptian plant Moringa peregrina exhibits cytotoxic exercises against breast malignancy mobile lines (MCF 7), colon mobile transport (HCT 116) [61]. Apigenin needs to be been demonstrated will make a standout among the gainful mixes for different phases about carcinogenesis [62].
- Curcumin's anticancer impact is should actuate apoptosis over cancellous units without cytotoxic impacts looking into solid units [63]. Curcumin modulates development about carcinogenic phones through regulation of different mobile indicating pathways including cell burgeoning pathway (Cyclin D1, c-Myc) [64].
- Saffron is an zest from the bloom of the saffron crocus what's more an nourishment colorant exhibit in the dry stigmas of the plant *Crocus sativus* saffron. Furthermore, its ethanolic extracts would also be accounted for the investigations around human lung malignancy pancreatic carcinoma cell transport skin carcinoma colorectal carcinoma units and breast malignant. Crocetin influences the growth of malignancy phones by hindering nucleic corrosive synthesis, upgrading antioxidative system, promoting apoptosis also upsetting development component indicating pathways.
- Gingerol needs to be concentrated onto its anticarcinogenic impacts for those malignant done colon, pancreas, breast, and ovarian. Gingerol needs to be exhibited antioxidant, anti-inflammation, and antitumor pushing properties (declines inducible nitric oxide synthase) [65].

CONCLUSION

In this review, we aimed to overview the breast cancer biomarkers and their development. A biomarker is an objectively measured characteristic that can be evaluated as an indicator of normal biological response, pathogenic processes, or therapeutic responses. Various types of screening methods are clinical and breast exams, mammography, hereditary screening, ultrasound, and attractive reverberation imaging. Certain plants and its constituents have been playing a major role in decreasing the activity of biomarkers such as Her-2, ER, PR, Cyclin-D1, and Cyclin E. Breast cancer is a heterogeneous disease with vast differences between patients in regard to treatment response and prognosis. Hence, strategies for individualizing care are required.

"Keep your sunny side up, keep yourself beautiful,
And indulge yourself!"

-Betsey Johnson.

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