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Review Article

Exploring human mammaglobin: as a possible diagnostic and prognostic indicator in breast cancer tissue

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ABSTRACT

Breast cancer is a major global health issue, with high diagnosis rates worldwide, especially in less developed areas, leading to significant mortality rates. This review focuses on the molecular characteristics of breast cancer, emphasizing the role of human mammaglobin-A (hMAM-A) as a diagnostic and prognostic marker. hMAM-A, a dimeric protein from the secretoglobin family, is produced exclusively by breast tissue and shows elevated levels in breast cancer cases, making it a highly accurate marker for disease detection. The review also examines various factors influencing breast cancer, such as age, tobacco use, menopausal status, and hormone replacement therapy (HRT). Younger age at diagnosis is associated with poorer outcomes, highlighting the importance of early detection. Tobacco smoke increases mortality rates in breast cancer patients. Menopausal status affects molecular subtypes and risk factors, impacting treatment and prognosis. HRT has a complex relationship with breast cancer risk. The review concludes by discussing the need for novel biomarkers, including hMAM-A, to improve breast cancer diagnosis and management.

Keywords: Mammaglobin-A, Breast cancer, Prognosis, Tobacco

INTRODUCTION

Breast cancer is a significant global health issue, being the most frequently diagnosed cancer globally, with around 2.26 million cases reported in 2020. It stands as the primary cause of cancer-related deaths among women. In 2020, it was observed that more than half of breast cancer cases and about two-thirds of breast cancer-related deaths occurred in regions with lower levels of development, despite the previous belief that the disease mainly impacted developed nations.[1]

Breast cancer is a complex disease with diverse molecular features, divided into three main subtypes based on hormone receptor (ER and PR) and HER2 (ERBB2) status: luminal ER-positive and PR-positive, further categorized as luminal A and B. HER2-positive, and triple-negative breast cancer (TNBC). At present, screening initiatives are essential in the fight against breast cancer, playing a significant role in decreasing mortality rates linked to this disease.[2]

The human breast is a unique exocrine gland located in the skin and subcutaneous tissue, consisting of breast parenchyma including ducts and lobules, surrounded by a supportive structure that includes fat and lymphatic vessels, all interconnected with a complex network of ligaments, nerves, arteries, and veins.

The mammary glands receive nerve supply from sympathetic and sensory fibers stemming from the 4th–6th thoracic nerves. To investigate the innervation of the mammary gland in rabbits, researchers utilized anatomical, electrophysiological, and histochemical techniques to observe catecholamine and cholinesterase staining, primarily indicating sympathetic adrenergic fibers. Results indicated that the papillary smooth muscle is innervated by sympathetic nerves positioned between the media and adventitia of all arteries, without providing innervation to glandular tissue. Moreover, nerve fibers containing butyrylcholinesterase (bacha), rather than acetylcholinesterase (AChE), also innervate blood vessels and papillae. The presence of adrenergic fibers in the papilla and blood vessels suggests a close association with BChE-containing fibers, indicating a significant proportion of the latter originates from the sympathetic system. Most mammary nerves travel alongside arteries and arterioles, with some sensory nerve fibers branching out from the arterial network to encircle the walls of mammary ducts for monitoring milk pressure. Currently, there is no documented neural supply to secretory cells, myoepithelial cells, or an innervated sphincter at the duct opening. Conversely, numerous adrenergic and sensory nerves are found surrounding mammary glands.[3]

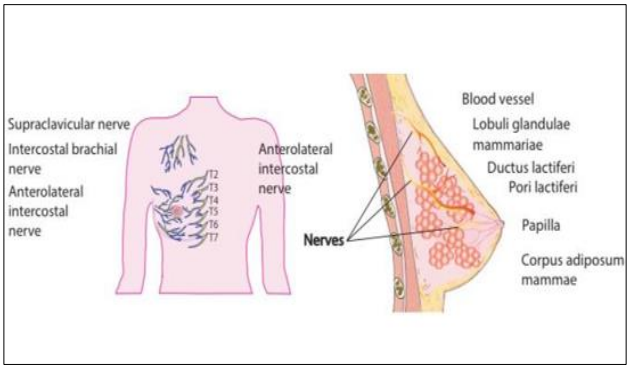

Figure 1: Nerve system in normal breast tissue. Anatomy of the breast and nerve fibers inside, T2-7 indicate the 2nd to 7th thoracic nerves: yellow, nerve fibers: red, blood vessels.

Of all cases of breast cancer, germ-line mutations in BRCA1/BRCA2 account for about 5%.

These mutations impact genes that act as tumor suppressors and play essential roles in DNA repair, regulating the cell cycle, and maintaining chromosomal stability. Cancers with impaired BRCA1/BRCA2 proteins struggle to mend DNA double-strand breaks, making them vulnerable to DNA-damaging agents like platinum, alkylating agents, anthracycline, or PARP inhibitors.

In patients diagnosed with breast cancer, the tumor features vary based on the presence of mutations in BRCA1 or BRCA2. BRCA1 mutation carriers often present with triple-negative breast cancer (TNBC), while those with BRCA2 mutations are inclined to have tumors expressing estrogen receptor (ER) and progesterone receptor (PR). Factors like tumor stage, grade, and molecular subtype play a role in determining the choice of adjuvant chemotherapy for individuals with BRCA mutations.

The current information on the predictive and prognostic importance of BRCA mutations in patients with non-metastatic breast cancer is inconsistent. Although individuals with BRCA mutations and triple-negative breast cancer may exhibit heightened sensitivity to DNA-damaging treatments, this increased sensitivity does not always result in improved survival outcomes.[4]

Mammaglobin-A was identified as one of the proteins that differs in expression between breast cancer and healthy breast cells by scientists in 1998. Mammaglobin-A, a member of the uteroglobin/Clara cell protein family, is one of around 20 similar proteins known as secretoglobins, the precise roles of which are still unknown. Scientists believe that these proteins play roles in cell signaling, immune response, chemotaxis, and potentially act as carriers for steroid hormones in humans. Mammaglobin-A, specifically, has the ability to bind steroid-like molecules. Mammaglobin-A, which is comprised of 93 amino acids, is produced by the SCGB2A2 gene located on chromosome 11q12. Its primary expression in normal tissues is found in the mammary gland, where it is frequently upregulated.

Mammaglobin-A is considered a possible target for therapy in cases of breast cancer. The debate surrounding the impact of increased mammaglobin expression on the severity of breast cancer varies, with some studies suggesting it promotes tumors, others suggesting it suppresses them, and some showing no discernible effect. Due to its specific presence in breast epithelial cells, the use of mammaglobin-A immunohistochemistry has become a commonly employed method for identifying metastatic breast cancer tissue. However, conflicting data exists regarding the prevalence of mammaglobin-A expression in tumors. Reported rates of mammaglobin-A positivity in breast cancer vary from 59 to 100% in lobular breast carcinomas and 25 to 94% in unspecified type invasive breast carcinomas. Moreover, immunohistochemical evidence of mammaglobin-A positivity has been noted in 11–76% of endometrial carcinomas, 37–100% of ovarian carcinomas, and 0–36% of prostatic adenocarcinomas.[5]

BACKGROUND

In 2018, leukemia was the main cause of death in Saudi Arabia and breast cancer the most common type of cancer diagnosed there. Also, the second cause of death There is growing evidence that Saudi Arabia has experienced a significant increase in breast cancer incidence, despite the country's far lower incidence than many Western countries.[6]

Breast cancer poses a significant challenge for women of a young age, impacting patients, families, and healthcare professionals alike. While the occurrence of breast cancer is less frequent in women under 40, its impact can be more profound compared to older individuals. This is due to its tendency to manifest at advanced stages with aggressive characteristics, necessitating more intense treatments like chemotherapy and mastectomy than those in their forties.[7]

Breast cancer cells have a notable increase of mammaglobin, which suggests that this protein may be an effective indicator for the breast cancer. Its presence in peritumoral tissue and the bloodstream indicates potential applications in various clinical settings.

Mammaglobin, found in two forms referred to as mammaglobin-A (MAM-A) and mammaglobin-B (MAM-B), serves distinct functions in the realm of cancer biology. MAM-A, predominantly found in breast tissue, is identified in approximately 80% of breast tumors, displaying an elevated expression level that can be up to 10 times greater than that in normal breast tissue.[8]

HUMAN MAMMAGLOBIN A AS A DIAGNOSTIC INDICATOR

The study aimed to evaluate the diagnostic precision of serum mammaglobin-A in distinguishing between benign and malignant breast tumors, given its specific production by breast tissue and elevated levels exclusively associated with breast cancer.

Human mammaglobin A (hMAM) has been recently recognized as a diagnostic marker for breast cancer and is predominantly expressed in breast tissue. It is a dimeric protein from the secretoglobin family and is linked with lipophilin B, secreted by breast epithelial cells. With a transmembrane domain and a signal peptide, MAM is released into circulation when the peptide is cleaved. Although its exact function is not fully understood, various studies suggest its involvement in cancer development, immune system regulation, and the transport of aromatic molecules like steroid hormones. Research indicates that MAM levels remain normal in other types of cancer, highlighting its specificity to breast cancer. Mammaglobin has demonstrated high accuracy in disease detection, with a sensitivity of 81.5% and a specificity of 100% at a threshold of 11.89 ng/ml. MAM's positive predictive value is 100%, surpassing that of CEA and CA 15–3. Moreover, among the three markers, mammaglobin exhibits the highest specificity at 100%.[9]

Three prior immunohistochemical studies have demonstrated a link between elevated levels of MAM-A protein expression and the status of ER and PR, as well as low tumor grade and absence of axillary node invasion. These findings indicate that breast cancer cases displaying increased mammaglobin-A expression are likely to be associated with less aggressive tumor characteristics.[10]

HUMAN MAMMAGLOBIN A AS A PROGNOSTIC INDICATOR

MAM has emerged as a promising biomarker for breast cancer due to its increased presence in both primary and metastatic breast cancer tissues and its specific association with mammary tissue. Extensive research indicates elevated levels of MAM in a significant portion of breast carcinomas, with differences noted depending on tumor subtype and stage. Its minimal expression in other cancers enhances its attractiveness as a distinctive biomarker for breast cancer. The link between high MAM expression and unfavorable prognostic factors suggests its involvement in the development and advancement of the disease.

This review aims to elucidate the role of MAM, a promising biomarker in the realm of breast cancer. It delves into MAM's presence in tumor and surrounding tissues, its levels in the bloodstream, and its significance in cancer advancement and spread. With its potential as a non-invasive diagnostic tool, MAM has the capability to transform early cancer identification, prognostic assessment, and treatment planning.

Table 2 provides a summary of MAM-A expression and various aspects of breast cancer relationships. The table classifies important prognostic elements such as tumor subtype and stage, hormone receptor status, tumor grade, cell proliferation, and peritumoral expression. It details the relationship between these factors and the expression of MAM-A, emphasizing the influence of different expression levels on the development and advancement of the illness. This summary emphasizes the potential significance of MAM-A as a notable biomarker in diagnosing and predicting outcomes in breast cancer.[8]

Table 1: Mammaglobin-A expression and correlation with breast cancer prognostic factor.

Prognostic factor	Mammaglobin-A expression
Tumor subtype and stage	Variable expression with positivity rates ranging from 59% to 100% for lobular breast carcinomas and 25% to 94% for invasive breast carcinomas
Hormone receptor status	Elevated levels correlate with estrogen receptor (ER) and progesterone receptor (PR) status
Tumor grade	High tumor grade associated with overexpression of hMAM
Cell proliferation	Higher Ki-67 proliferation index observed in hMAM-positive invasive breast cancer
Peritumoral expression	Presence detected, suggesting a possible link with local invasion, metastasis, and aggressive disease phenotypes

COMPARISONS WITH OTHER BIOMARKERS

MAM is a protein present in breast tissue and also detectable in the bloodstream. MAM has been suggested as a biomarker for the detection of breast cancer (BC), as patients show elevated levels of this protein in both their serum and tumor tissue compared to individuals without the disease.[11]

Studies are concentrated on discovering novel biomarkers with improved sensitivity, specificity, and tissue specificity. Human mammaglobin (hMAG), a hopeful contender, is presently being studied for its possible usefulness in diagnosing and predicting the outcome of breast cancer. Comparative evaluation of human mammaglobin with other markers for breast cancer.

hMAG

hMAG demonstrates elevated levels of expression (80–90%) in breast tumors and is notably effective (97%) in identifying any remaining disease.

ER

It is present in primary lung adenocarcinomas, ER is utilized to anticipate responses to hormonal therapy in breast cancer, although its prognostic value is restricted.

PR

PR is deemed a crucial element in hormonal treatment.

BRAC-1 and BRAC-2

BRAC-1 and 2 stands for breast cancer 1 and 2, early onset, and can aid in the identification of patients at high risk.

5-Ki67

It is believed to serve as a marker for the advancement of breast cancer.[8]

FUTURE DIRECTIONS AND RESEARCH GAPS

MMA-A was discovered in 1998, hMAM-A is among the proteins that exhibit distinct expression patterns in breast cancer compared to normal breast tissues. Part of the uteroglobin/Clara cell protein family, MMA-A is one of more than 20 related proteins called secretoglobins. The precise function of secretoglobins is not fully understood, but they are thought to be involved in cell signaling, immune responses, chemotaxis, and potentially serve as transporters for steroid hormones in the human body.[5]

Certain research suggests that even when tumor cells are not present in lymph nodes or bone marrow, circulating tumor cells (CTCs) can still be found in the peripheral blood (PB) of individuals. Breast cancer is a systemic condition where tumor cells can disseminate to the blood and lymphatic system in the initial phases. Given the convenience of obtaining blood samples, PB samples have been utilized as targets for detecting and assessing the prognosis of breast cancer. Common biomarkers in breast cancer such as CA153, CA27.29, and HER2/neu show variability in expression among patients due to tumor heterogeneity. Therefore, the search for a new biomarker with high sensitivity and specificity is crucial for accurate diagnosis and prognosis assessment in breast cancer cases. Discovered in 1996 through a differential polymerase chain reaction by Watson and Fleming, MMA-A consists of 93 amino acids and belongs to the secretory protein family. MMA-A is overexpressed in 40–80% of primary and metastatic breast carcinoma cases.[12]

AGE

Breast cancer diagnosed before the age of 40 is linked to poorer outcomes and more advanced stages of the disease. Women under 40 tend to have more aggressive tumor characteristics and experience worse clinical results. In the United States and Europe, the average age of breast cancer diagnosis is 63, with 19% of cases occurring in those under 50 and only 5% under 40. However, in Arab countries and many low- or middle-income nations, 50% of breast cancer patients are diagnosed before 50, and 20.8% are under 40.[13]

The average age of diagnosis for breast cancer in Saudi women was 50 years, with cases ranging from 14 to 108 years. The highest number of breast cancer cases occurred in the age group of 45-49, with 356 cases. In the Gulf Cooperation Council region, 25.5% of breast cancer cases were found in women under 40 years old. A study revealed an average age of breast cancer diagnosis of 50.6 years in Gulf countries, contrasting with 60 years in Western nations.[14]

In study made in Saudi Arabia found the number of breast cancer cases increased by 186% from 783 cases in 2004 to 2240 cases in 2016. A total of 18,970 breast cancer cases were recorded over the 13 years (Figure 2). The ASR increased from 15.4 in 2004 to 27.2 per 100,000 women in 2016. This increasing trend was statistically significant at an APC of +3.7 (95% CI=2.3 to 5.1) per year.

Incidence according to age at diagnosis in Saudi Arabia

The median age at diagnosis was found to increase from 47 years in 2004 to 50 in 2013, 2014, and 2016. This increasing trend was statistically significant at an APC of 0.7 (95% CI = 0.5 to 0.9) per year (Figure 3). The results showed that almost 60% of breast cancer cases were diagnosed among women aged 40–49 years (31.8%) and among women aged 50–59 years (29.8%) (Table 1). For age-specific incidence, the highest APC was seen in women aged 70–74 years (APC= +7.6, 95% CI=4.7 to 10.7), whereas the lowest was seen in women aged 45–49 years (APC= +2.3, 95% CI=0.4 to 4.3).[15]

TOBACCO

Cigarette smoke is a significant human carcinogen linked to higher mortality rates in breast cancer cases, although its impact on breast cancer occurrence is not as consistently established. Cigarette smoke comprises various chemicals known for their carcinogenic and hormonal effects, and its influence on mammographic density characteristics remains unclear.[16]

Persisting with smoking following a cancer diagnosis can heighten the chances of overall mortality, cancer relapse, and adverse effects during treatment. Ceasing smoking promptly can mitigate these risks and enhance survival rates. Despite the advantages of quitting smoking, research indicates that as many as half of cancer patients continue to smoke post-diagnosis. A study focused on female breast cancer patients revealed that merely 17% of those who smoked reported cutting down or quitting smoking within a year of undergoing breast cancer treatment.[17]

In this research, 54,614 women diagnosed with breast cancer participated, with 1687 being smokers and 52,927 non-smokers. Table 1 displays a comparison of baseline characteristics between women who smoked and those who did not among the breast cancer patients. Significant variations were observed in age, clinical stages, alcohol consumption, betel nut use, CCI score, and BMI between smoking and non-smoking women with breast cancer.[18]

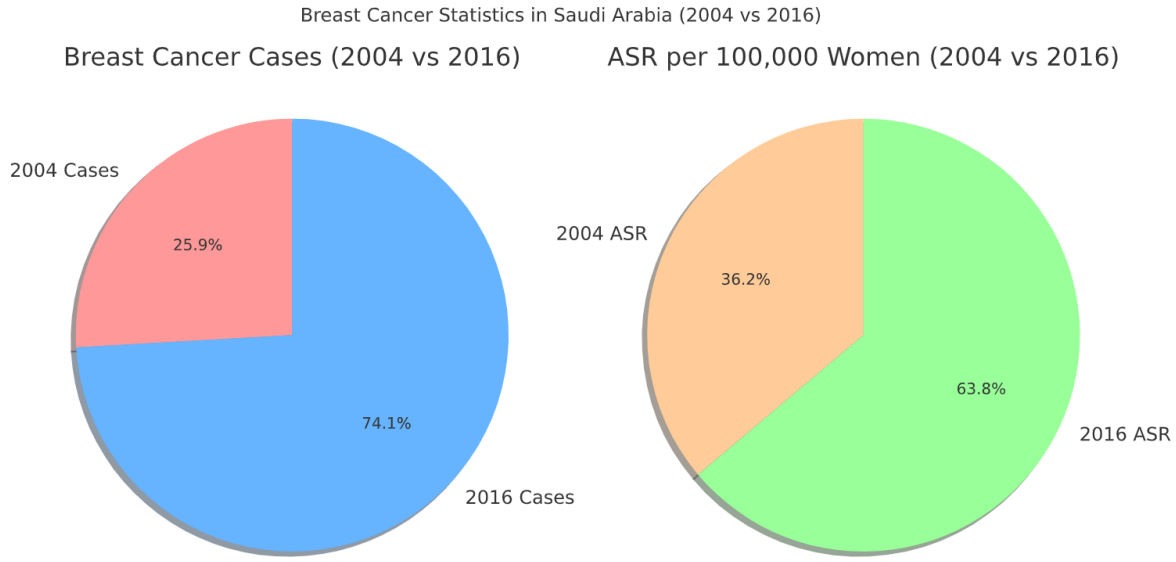

Figure 2: Joint point regression analysis of breast cancer incidence in Saudi Arabia (2004-2016).

Cl=Confidence interval at zero join points, ASR: age-standardized rate, APC: annual percent change. Indicates that the APC is significantly different from zero at p=0.05

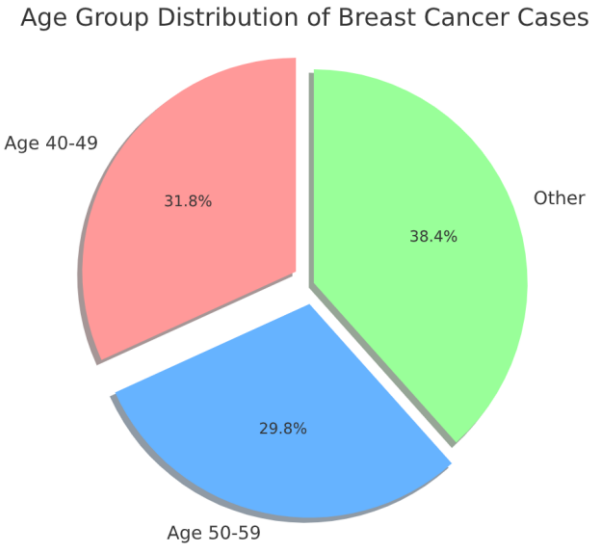

Figure 3: Number of breast cancer and median age at diagnosis in Saudi Arabia, 2004-2016.

APC: Annual percentage change, indicates that the APC is significantly different from zero at p=0.05, Cl= confidence interval at zero joint point

Table 2: Average ASR, total number of cases and the APC among Saudi female by age group. 2004-2016.

Age group (years)	ASR (average)	Total number of cases (2004-2016)	APC	95% CI
30-34	13.8	1254	1.6	-0.6 to 3.8
35-39	25.8	2050	1.0	-0.7 to 2.7
40-44	43.0	2763	1.4	-0.2 to 3.0
45-49	61.1	3148	2.3*	0.4 to 4.3
50-54	65.6	2712	5.7*	4.4 to 7.1
55-59	66.0	2025	4.8*	2.5 to 7.1
60-64	64.4	1476	3.5*	1.1 to 5.9
65-69	63.3	1033	6.0*	1.5 to 10.7
70-74	66.4	801	7.6*	4.7 to 10.7
75+	52.8	879	6.3*	4.6 to 8.1

ASR: age-standardized rate. APC: annual percentage of change. CI: Confidence interval

Table 3: Baseline characteristics between smokers and non-smokers among women with breast cancer.

Variables	Non-smokers (n=52,927)	Smokers (n=1687)	P value
Age group (years), N (%)			
<45	9681 (18.29)	509 (30.17)	<0.0001
45-54	16.705 (31.56)	676 (40.07)	
55-64	15,118 (28.56)	335 (19.86)	
≥65	11,423 (21.58)	167 (9.90)	
Clinical stage, N (%)			
I	19,578 (36.99)	551 (32.66)	0.0042
II	24,368 (46.04)	827 (49.02)	
III	5195 (9.82)	178 (10.55)	
IV	3786 (7.15)	131 (7.77)	
Drinking alcohol, N (%)	1770 (3.34)	553 (32.78)	<0.0001
Chewing betel nuts, N (%)	152 (0.29)	90 (5.33)	<0.0001
CCI, N (%)			
0	38,854 (73.41)	1317 (78.07)	0.0004
1	7401 (13.98)	203 (12.03)	
2	3628 (6.85)	92 (5.45)	
3	1536 (2.90)	32 (1.90)	
>3	1508 (2.85)	43 (2.55)	
BMI, N (%)			
<18.5	2291 (4.33)	130 (7.71)	<0.0001
18.5-25	30,228 (57.11)	1021 (60.52)	
25-30	15,162 (28.65)	384 (22.76)	
30-35	4176 (7.89)	124 (7.35)	
≥35	1070 (2.02)	28 (1.66)	
Death, N (%)	6069 (11.47)	211 (12.51)	0.1872
Death within 5 years, N (%)	5470 (10.35)	191 (11.32)	0.1905
Death due to breast cancer, N (%)	4536 (8.57)	167 (9.90)	0.0554
Comorbidity, N (%)			
Myocardial infarction	97 (0.18)	5 (0.30)	0.2488
Congestive heart failure	525 (0.99)	12 (0.71)	0.2502
Peripheral vascular disease	186 (0.35)	8 (0.47)	0.4040
Cerebrovascular disease	1486 (2.81)	36 (2.13)	0.0979
Dementia	476 (0.90)	7 (0.41)	0.0364
Chronic pulmonary disease	1804 (3.41)	78 (4.62)	0.0071
Renal disease	1136 (2.15)	23 (1.36)	0.0280
Hypertension	11,137 (21.04)	252 (14.94)	<0.0001
Hyperlipidemia	8131 (15.36)	184 (10.91)	<0.0001
Diabetes	6068 (11.46)	141 (8.36)	<0.0001
Liver disease	1368 (2.58)	42 (2.49)	0.8085

Continued.

Variables	Non-smokers (n=52,927)	Smokers (n=1687)	P value
Treatment, N (%)			
Operation	49,499 (93.52)	1574 (93.30)	0.7161
Radiotherapy	29,588 (55.90)	1007 (56.69)	0.0020
Chemotherapy	35,136 (66.39)	1240 (73.50)	<0.0001

MENOPAUSE STATUS

It is essential to differentiate the burden of breast cancer based on menopausal status for several reasons. Firstly, this type of hormonal cancer affecting the mammary gland presents distinct molecular characteristics and risk factors in premenopausal and postmenopausal individuals. For instance, while being overweight is a risk factor for Breast cancer that develops after menopause, its association with premenopausal cancer is less well-defined, with some studies indicating a potential inverse relationship. Secondly, the molecular subtypes of breast cancer, which vary in risk factors, treatment approaches, and prognosis, exhibit different age-related incidence patterns around the time of menopause. Thirdly, considering the public health viewpoint, the proportion of Based on their population demographics, countries differ greatly in the proportion of women at risk of postmenopausal versus premenopausal breast cancer. Fourthly, early detection of breast cancer poses challenges in premenopausal women due to breast density, often resulting in later-stage diagnoses. Lastly, the impact of breast cancer on affected women differs between younger and older patients. Therefore, examining the burden of breast cancer and its trends based on menopausal status is crucial for guiding preventive measures, detection strategies, and healthcare planning.[19]

The occurrence of estrogen receptor positive (ER+) breast cancer decreases during menopause as women experience a decline in natural estrogen and progesterone levels. In contrast, women undergoing hormone replacement therapy (HRT) receive supplemental estrogen and progesterone. Research from the Women's Health Initiative study revealed that women using HRT had notably higher chances of developing ER+ breast cancer.[20]

HORMONAL AND HORMONE REPLACEMENT THERAPY

Breast cancer is the leading type of cancer among women in the UK, with around 11,400 female deaths attributed to it annually. Thanks to early detection methods like screening and advancements in treatment, the majority of women diagnosed with breast cancer now have a higher chance of survival.

Data collected from The Million Women Study (MWS) raised questions regarding the potential risks associated with hormone replacement therapy (HRT) over an extended period, particularly in relation to breast cancer.

Analysis of the MWS has revealed numerous significant shortcomings in both the research approach and results, ultimately restricting the trial's capacity to definitively link HRT with breast cancer.[21]

A series of studies based on the women's health initiative (WHI) randomized trials on hormone therapy has unveiled detailed trends regarding the influence of hormone therapy on breast cancer susceptibility and outcomes. The trial that evaluated the combination of conjugated equine estrogen (CEE) with medroxyprogesterone acetate (MPA) demonstrated an initial rise in breast cancer risk over approximately 5.6 years of intervention, which was succeeded by a slight decline in this heightened risk. Nevertheless, a lasting adverse impact on breast cancer risk was noticeable over a total follow-up period of 13 years. In contrast, in the trial using CEE alone, the decrease in breast cancer risk observed over about 7.2 years of intervention endured throughout the 13-year cumulative follow-up period.

Results from recent observational studies on hormone therapy and breast cancer differ from the findings of randomized clinical trials, particularly regarding the utilization of estrogen alone. A significant correlation was discovered in a meta-analysis conducted by the collaboration group on hormonal factors in breast cancer between the use of estrogen alone or in combination with progestin and an increased risk of breast cancer.[22]

CONCLUSION

Breast cancer is a major global health concern, particularly in Saudi Arabia, where incidence rates are rising. Understanding the molecular characteristics, biomarkers, and risk factors associated with breast cancer is critical. hMAM-A shows promise as a diagnostic and prognostic biomarker due to its high specificity and sensitivity. Factors like age, tobacco use, menopausal status, and HRT significantly influence breast cancer development and progression. Early detection, lifestyle changes, and targeted therapies based on individual risk factors are essential. Future research should focus on validating hMAM-A's clinical utility, identifying novel biomarkers, and developing personalized treatment approaches for improved outcomes.

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