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Review Article

Tamoxifen and the Risk of Breast Cancer in Women With Different Types of Mutation

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The development of breast cancer (BC) is a multistep process in which different cells and genes are involved, and its prevention and treatment are challenging. If BC is detected in the early stages, it can be prevented and the survival rate is high, and vice versa. Growing studies show that in recent years, many advances have been made in the field of BC prevention and treatment. Tamoxifen (TAM) is one of the important drugs used in the treatment of BC. Research shows that stem cells and various genes have a key role in TAM drug resistance in BC. Therefore, in this study, we intend to clarify the genes that are involved in the resistance to TAM in BC and perhaps take a small step in the prevention and treatment of BC.

Keywords: breast cancer; drug resistance; mutation; tamoxifen

1. Introduction

Breast cancer (BC) remains one of the most commonly diagnosed malignancies among women and has stayed as a major public health concern for decades. At the cellular level, the disease results from unchecked division of abnormal breast cells, which may eventually invade nearby tissues or metastasize to distant organs. Current global data suggest that around one in four newly diagnosed female cancers are breast-related, placing it at the top of the list for cancer incidence in women [1]. In terms of mortality, it is second only to lung cancer among women in the United States.

This paper focuses on understanding several key dimensions of BC, its general characteristics, the influence of genetic factors on its progression, and the therapeutic significance of tamoxifen (TAM) [2, 3]. The variation of women diagnosed with BC in terms of age, ethnicity, and genetic backgrounds makes the understanding of the disease significantly challenging. BC is a disease that does not discriminate, affecting women of diverse ages, races, and ethnicity. Aging is a well-documented risk factor [4, 5]. Moreover, a family history, especially those with first-degree relatives, can significantly raise an individual's chances of developing the disease. This shows a clear hereditary influence. Even so, genetics alone do not account for all cases. Beyond genetic inheritance, several nongenetic factors can increase the risks of the disease. These include the timing of reproductive events and long-term hormone use, as well as

habits like alcohol consumption and eating habits [6]. Research efforts over the last few decades have gradually uncovered numerous genetic influences that appear to play a role in BC risk. Among the most well-known genes involved are BRCA1 and BRCA2. It is well known that these genes prevent tumor growth through improving genomic stability, in particular by their function in double-strand DNA repair. Mutations can disrupt these repair processes, increasing the frequency of mutations and, consequently, it will increase risk of breast and ovarian cancer. BRCA1 and BRCA2 are therefore frequently given priority in genetic screening procedures [7]. Another gene of considerable interest is TP53, which plays a regulatory role in the cell cycle and apoptosis. Germline mutations in TP53 are associated with Li–Fraumeni syndrome, a condition marked by susceptibility to a wide range of aggressive cancers, including breast malignancies diagnosed at younger ages [8]. The PTEN gene, which regulates how cells grow and survive, is another relevant factor. Mutations in this gene are known to underlie Cowden syndrome, which raises the risk of breast and other cancers [9]. Likewise, Ataxia-telangiectasia mutated (ATM)—a gene crucial for repairing double-strand DNA breaks—has been linked to increased susceptibility when inherited in a mutated form. A broader set of genes, including CHEK2, PALB2, RAD51C, RAD51D, STK11, and NBN, have also been implicated. But, their specific roles differ, most participate in DNA repair or cell-cycle regulation. Together they contribute to the complex genetic backdrop that influences BC development [10–12].

TAM—classified as a selective estrogen-receptor modulator (SERM)—has been widely adopted in the treatment of hormone-sensitive BC. First, it was approved for therapeutic purposes; however, it has also been used for preventive applications, especially for individuals identified as having high-risk profiles [13]. Its efficacy has been shown in both early-stage and long-term adjuvant treatments. TAM's role is not limited to therapy alone; its flexibility allows it to be applied in both preventive strategies and as an adjuvant treatment. BC management to address the disease's complexity involves a wide range of therapeutic approaches. Surgery, including procedures like lumpectomy and mastectomy, is the main method for removing tumors and minimizing the chance of recurrence. Radiation therapy, which targets malignant cells using high energy, aims at removing malignant cells, is commonly utilized after surgery as a supportive treatment or, in certain instances, as the main therapeutic approach. Chemotherapy offers a systemic treatment option by targeting rapidly multiplying cells across the body. Typically, it is given prior to surgery (neoadjuvant) to decrease tumor size or following surgery (adjuvant) to eliminate remaining cells. More recently, immunotherapy which stimulates the body's own immune defenses against cancer has gained attention as a novel strategy. In BC, specifically, research is ongoing to determine how immunotherapeutic methods may further improve patient outcomes [14, 15]. Hormonal therapy is just a single part of wide treatment. Meanwhile, drugs like trastuzumab that are used for human epidermal growth factor receptor 2 (HER2)-positive BC have shown promising results by precisely targeting molecular features of tumor cells. This limits side effects while improving results [16]. Although TAM remains a key option for hormone-sensitive cases, it now functions as part of a much broader and more individualized framework for BC care. The following sections will examine the relationship between genetic risk factors and TAM efficacy in greater depth, contributing to the broader effort to improve prevention and therapy through tailored interventions [17, 18].

2. BC and Its Related Risk Factors

BC is one of the most common cancers and ranks second in terms of mortality rate [19]. The progression of BC involves multiple types of cells and is a complex process. Preventing BC poses significant challenges worldwide [20, 21]. Early identification of the disease can result in a favorable prognosis and increased chances of survival. In North America, timely diagnosis of BC has contributed to a 5-year relative survival rate exceeding 80% for patients [22]. BC is categorized into distinct molecular subtypes according to the expression of hormone receptors and growth factor receptors [23]. This disease is divided into four categories (luminal A, luminal B, HER2, and triple-negative BC (TNBC)) based on progesterone and estrogen receptors (ERs) and HER2 overexpression. BC doctors target most of these receptors to provide targeted therapies [24, 25]. BC is among the prevalent types of cancer that can be influenced by inherited genetic mutations found in genes like p53, CHEK2, BRCA1, BRCA2, and others. Furthermore, recent research has revealed that certain genes, such as BRCA1, BRCA2, PALB2, STK11, TP53, PTEN, and CDH1, carry a substantial risk for developing BC, with an odds ratio greater than 5.0 [26]. Various genetic and environmental factors such as lifestyle, sex, age, time of onset of menstruation, ionizing radiation, use of steroid drugs, and genetic mutations have an effect on the occurrence of BC [27]. Although numerous factors that elevate the likelihood of developing BC have been identified, approximately 75%–80% of women do not exhibit any identifiable risk factors for the disease [4]. Early detection plays an important role in the prognosis and treatment of BC because it reduces the probability of death from this disease. Common diagnostic methods for BC include mammography, magnetic resonance imaging (MRI), and precision positron emission tomography (PET). These methods are used to evaluate the treatment response and spread of tumors. In recent years, microwave imaging (MI) has emerged as a cost-effective and safe diagnostic option for BC [28, 29]. Treatment decisions are based on factors such as BC grade, stage, and molecular type to provide personalized, safe, and effective care. The stage of BC determines the spread and severity of the disease within the body. It is categorized using the TNM system, which considers factors such as tumor size, lymph node involvement, and the presence of metastases [30]. For BC that has not spread to other parts of the body (nonmetastatic BC), treatment approaches may involve complete surgical removal of the tumor, breast-conserving procedures with radiation therapy given before (neoadjuvant) or after

(adjuvant) surgery, as well as systemic therapies like chemotherapy and targeted therapy. In cases of metastatic BC, the primary objective is to manage the spread of the tumor as this type of BC remains incurable. Similar systemic therapies are employed for the treatment of metastatic BC. BC treatment challenges include addressing treatment resistance and relapse. About 30% of early BC cases experience a recurrence, often in the form of metastasis [31]. Therefore, the development of new strategic therapies is essential for the effective treatment of each BC subtype [32]. In recent years, significant progress has been achieved in discovering novel medications for treating BC. A better comprehension of the biological diversity within BC has enabled the development of a more efficient and personalized treatment approach [24, 33]. TAM, a selective modulator of ER, has emerged as one of the most widely used hormonal drugs in this class. Recent studies have demonstrated the potential benefits of combining TAM with other hormonal medications for the treatment of ER-positive BC [34]. Figure 1 visually summarizes the key elements linked to BC, including risk factors, prevention, screening, treatment options, and biological modifiers. The diagram highlights different risk factors involved in BC onset and outlines the main management strategies, such as early detection through screening, various treatment approaches like surgery and targeted therapies, as well as preventive interventions including chemotherapy and biological treatments.

3. Types of Mutations That Cause BC

As for BC development, environmental factors and genetics play a significant role besides family history in determining BC risk [35]. For people with a family history of BC, a specific predisposing gene is identified in less than 30% of cases. More than 25% of hereditary cases are related to high penetrant genes such as TP53, PTEN, BRCA1, BRCA2, CDH1, and STK11 [36]. Figure 2 illustrates TAM's mechanism of action and the major signaling pathways involved in BC progression and TAM resistance. TAM, as an endocrine therapy, blocks ER signaling in BC cells, thereby inhibiting estrogen-driven transcription and cellular proliferation. The figure highlights key downstream pathways activated by estrogen–ER complexes, including the Ras/RAF/MEK/ERK and PI3K/AKT/NFκB cascades, which promote antiapoptotic effects, autophagy, and tumor progression. Cross-talk with growth factor receptors (HER2, EGFR, and IGF-1R) further enhances these pathways, contributing to resistance mechanisms. The diagram emphasizes the complexity of TAM response and the interplay between genetic and molecular factors in BC management.

3.1. BRCA. BC gene (BRCA) proteins transcript the regulation and DNA recombination. These proteins are vital in the DNA damage response, which is an essential pathway that ensures the survival of normal and malignant cells [7, 37]. The key player associated with BC is the mutation of BRCA1 and BRCA2. These genes account for about 15%–16% of all hereditary BC [38–40]. Females with BRCA1 or BRCA2 mutation are at risk of BC of 50%–85%. The risk of BC in men with BRCA2 mutation is 5%–10% [36]. Women with BRCA1 and BRCA2 mutations are at 65%–85% higher risk of developing invasive BC and 15%–65% risk of developing invasive ovarian cancer [41]. The BRCA1 is located on chromosome 17q21, and BRCA2 is mapped to chromosome 13q13. BRCA2-related tumors are mostly sporadic tumors. Genetic testing for BRCA1 and BRCA2 mutations can help identify individuals at high risk for developing BC and also helps as a means for screening and management plans [7]. Regarding the connection between BRCA1/2 and TAM, TAM has been shown to reduce the incidence of BC in women who have mutations in BRCA1/2 [42].

3.2. TP53. The mutation of TP53 disturbs the growth and division of the cells. Mutation in TP53 can result in triple-negative BC, which is the most aggressive type of BC [38]. This type of BC is more likely distributed to other parts of the body. Li–Fraumeni syndrome is a rare inherited disorder that the mutation of TP53 can cause. For individuals with Li–Fraumeni syndrome, the incidence of BC at the age of 50 is 50%–80% compared to the general population, which is 13%. These findings contribute to future studies for management and treatment programs [43]. Not all BCs are related to the latter genes, and 2%–3% of BCs are due to low penetrance genes such as CHEK2, NBS1, RAD50, BRIP1 (BACH1), ATM, and PALB2 [36, 38]. Studies have shown that mutations in TP53 disrupt the effectiveness of the drug TAM in luminal BC and cause drug resistance [44].

3.3. CHEK2. The most common mutation is CHEK2, which accounts for 1%–2% of the population. CHEK2 is a protein kinase that stabilizes p53 and interacts with BRCA1 after activation [36]. CHEK2 plays a key role in DNA repair and cell-cycle regulation as being the tumor suppressor gene. Interestingly, CHEK2 mutation leads to a 10-fold increase in BC in men and a two-fold increase in BC in women [41, 45]. Notably, there is no additional increase in risk for carriers of the CHEK2 and BRAC1 or BRACK2, which is most likely due to an overlapping effect on DNA repair. The mutation of CHEK2 is more common in women of Ashkenazi Jewish descent. In this regard, women of Ashkenazi Jewish descent with a CHEK2 mutation have a 10- to 15-fold enhancement prevalence of BC in comparison to the other women. According to some studies of mutations in the CHEK2 gene in ER^+ BC, TAM is effective in reducing the risk of BC and reducing disease recurrence [45].

3.4. BRIP1. BRCA1-interacting protein C-terminal helicase 1 (BRIP1) is a DNA helicase and DNA-dependent ATPase responsible for DNA repair and tumor suppressor function of BRCA1 and helps maintain genomic stability. The BRIP1 gene is located on chromosome 17q21. BRIP1 encodes a protein that interacts with BRCA1 [46]. The BRIP1 mutation accounts for less than 1% of BC cases [36, 47, 48]. Interestingly, the BRIP1 mutation is associated with Fanconi

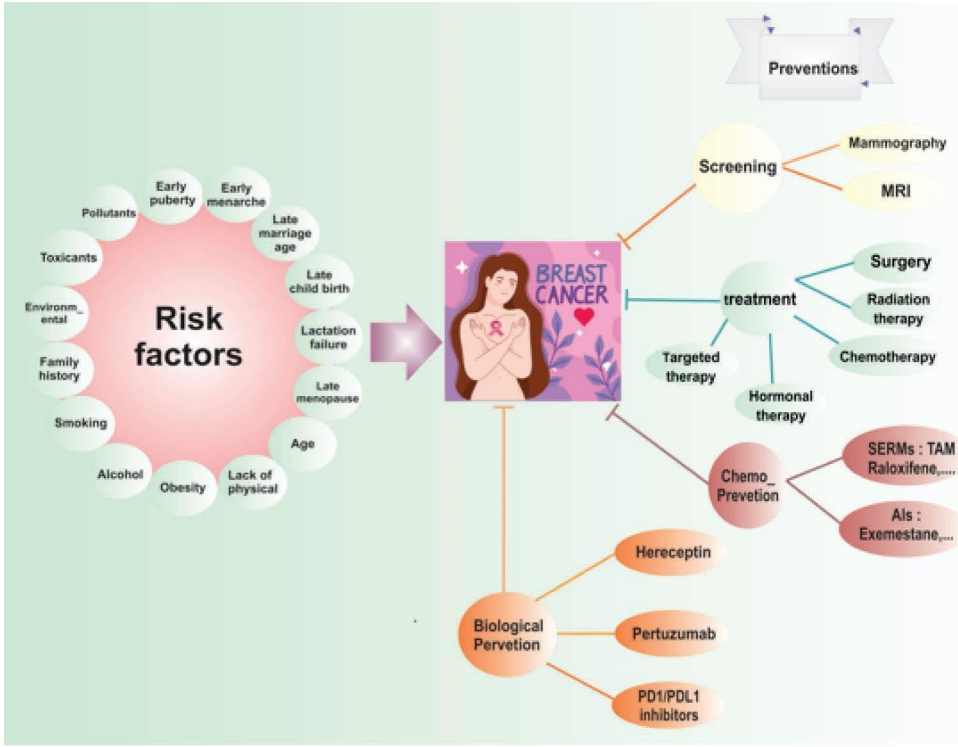

Figure 1: An overview of BC, from risk factors to management strategies. The figure includes key risk factors (such as early onset of puberty, family history, and smoking), preventive strategies, screening methods (like mammography and MRI), treatment modalities (including surgery and chemotherapy), and the use of biological agents (such as Herceptin and pertuzumab).

anemia, in which the bone marrow fails and the body is predisposed to cancer [49]. A study by Kharrati-Koopaee et al. regarding the relationship between BRIP1 gene expression and the drug TAM revealed that there is no significant relationship between BRIP1 gene expression and the drug TAM in BC cells [50].

3.5. ATM. ATM is a protein kinase conflicted in repairing dsDNA and regulates BRCA1 and CHEK2 and is a fifth DNA repair gene, together with BRCA1, BRCA2, TP53, and CHEK2, involved in BC predisposition. The ATM gene encodes a protein vital for DNA repair and cell-cycle regulation. The ATM gene is located on chromosome 11q23 [51]. Mutation of the ATM gene can result in ataxia-telangiectasia (AT) [45]. This progressive neurological degenerative disorder increases the risk of cancer, especially BC, by 2- to 13-fold, with a higher risk under 50 years old. According to studies, the relative risk of BC via the mutation of ATM is 2.3, which is mainly seen in women under the age of 50 [36]. Though the exact mechanism of how ATM mutation can increase the risk of BC is not yet completely understood, the accumulation of genetic mutations can promote cancer development [45, 52]. Studies have shown that ATM BC is mostly endocrine-positive, dedifferentiated, and more aggressive with poor diagnosis.

3.6. PALB2. The partner and localizer of the BRCA2 (PALB2) gene is located on chromosome 16 [53]. PALB2-encoded protein is associated with BRCA2 and responsible for supporting BRCA2 stability and its localization in the nucleus after DNA damage [54]. PALB2 and BRCA2 are tumor suppressors interacting with DNA repair [45, 55]. The PALB2 mutation is responsible for 1%–2% of BC. Women with PALB2 mutations have a 2- to 4-fold increased risk of developing BC in contrast with other women in general populations. In addition to BC, the PALB2 mutation also can develop ovarian cancer [56, 57]. Notably, the biallelic inactivation mutations in PALB2 can result in Fanconi anemia, characterized by a predisposition to pediatric malignancies such as AML and Wilms tumor [54]. A study on the relationship between the PALB2 gene and TAM showed that taking the drug TAM increases the expression of the PALB2 gene [50].

3.7. PTEN. PTEN is a tumor suppressor localized to chromosome 10q23 and essential for cell regulation, growth, and migration. PTEN is key in modulating the 1-phosphatidylinositol 3-kinase (PI3K) pathway related to cell proliferation and survival. PTEN suppresses BC growth through downregulation of PI3K [58]. The germline mutation of PTEN can result in Cowden syndrome, a disorder known for developing multiple hamartomas and increasing the risk of cancer, including BC [59]. It is said that one-third to one-half of women who have Kadon's disease as a result of PTEN gene mutation develop BC. However, only 5% of BC is due to PTEN mutation [58, 60]. The loss of PTEN protein expression is related to lymph node metastasis. The risk of having BC in women with Cowden syndrome is 85% by age 85 years compared to women in the general population [59].

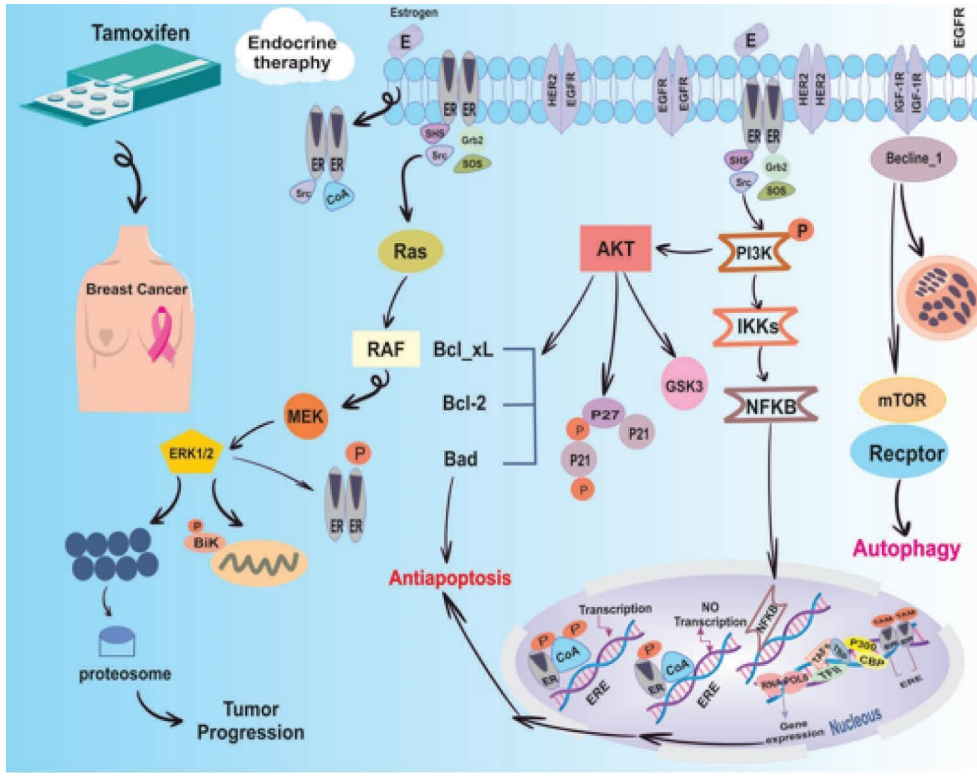

FIGURE 2: Schematic representation of TAM's mechanism of action and the major signaling pathways involved in BC progression and TAM resistance. TAM, as an endocrine therapy, inhibits estrogen receptor (ER) activity in BC cells, blocking estrogen-driven transcription and cellular proliferation. The diagram illustrates how estrogen–ER complexes activate downstream pathways—including Ras/RAF/MEK/ERK and PI3K/AKT/NFκB—leading to antiapoptotic effects, autophagy, and tumor progression. Cross-talk with growth factor receptors (HER2, EGFR, and IGF-1R) and dysregulation of apoptosis, cell cycle, and gene expression contribute to resistance mechanisms, highlighting the complexity of therapeutic response in genetically diverse BC.

Various studies have been conducted on the relationship between the PTEN pathway and the drug TAM, and these studies have proven that the use of TAM reduces PTEN gene expression and that increasing PTEN pathway expression sensitizes BC cells to TAM [61, 62].

3.8. RAD51. RAD51C and RAD51D are necessary for DNA repair that function as tumor suppressor genes. Mutation in these genes can lead to hereditary ovarian cancer and BC. Women with the mutation of RAD51C or RAD51D are at a higher risk of about 20%–40% of BC [10]. The mutation of RAD51C and RAD51D accounts for 1%–2% of all BC cases. Like TP53, the mutations of RAD51C or RAD51D are associated with the aggressive type of BC, which is triple-negative and less likely responsive to treatment [10, 63]. There have been no clear studies regarding the relationship between the RAD51 pathway and TAM, but according to some studies, increased RAD51 expression by increasing the DNA repair pathway may increase resistance to the TAM drug [64].

3.9. STK11. Serin/threonine kinase gene (STK11), also known as LKB1, is a tumor suppressor on chromosome 19p that plays many roles in cell biology at cytoplasmic and nuclear localization. It is a key protein kinase that regulates cell-cycle arrest, p53-mediated apoptosis, and energy metabolism [65]. As a result of STK11 mutation, it can cause Peutz–Jeghers syndrome (PJS) [65, 66]. PJS is a rare disorder of developing hamartomatous polyps in the gastrointestinal tract and mucocutaneous pigmentation, which can gradually lead to the development of various cancers, including BC [67, 68]. The risk of developing BC in patients with PJS is 8% at the age of 40% and 45% by the age of 70. In this regard, the loss of STK11 expression leads to papillary breast carcinoma. Therefore, it is a great candidate for BC studies. Women with STK11 mutation are 54% more at risk of developing BC in contrast with women in the general population. Research shows that in people with the STK11 mutation, the drug TAM and other estrogen-blocking drugs reduce the risk of BC [67, 69].

3.10. NBN. The NBN gene is located on chromosome 8q21. NBN is a protein involved in nonhomologous end joining (NHEJ), which is a key way to repair double-strand breaks in DNA, and nibrin, which the NBN encodes, is responsible for DNA repair. The mutation of NBN causes the impairment of cell repair for DNA damage and, finally, the accumulation of genetic mutations and cancer development [70–72]. Women with NBN mutation are at a 2- to 4-fold increased risk of developing BC in comparison to the women in the general population. According to the studies, NBN mutation

accounts for 1%–2% of all BC cases [70, 73]. Mutation in the NBN gene can result in Nijmegen breakage syndrome (NBS), which may result in various diseases, particularly cancer, including BC [72]. NBN mutations are also associated with the development of ovarian cancer. As for the mechanism, the NBN mutations increase the risk of BC through DNA double-strand breaks (DBS) [74]. About 70% of BCs are ER-positive (ER^+). Studies have shown that ESR1 mutations work in favor of tumor progression; therefore, they influence metastasis [75].

4. TAM in the Treatment of BC

TAM is a SERM that is proven to be effective in treating ER^+ BC in premenopausal women [76]. TAM reduces the risk of ER^+ BC in women with an increased risk of approximately 37% and also reduces the risk of BC in females with BRCA1 or BRCA2 mutation [77]. The low incidence of side effects made this drug suitable as an adjuvant therapy for women with node-positive BC. TAM also provides the benefit of recurrence prevention and survival advantage for postmenopausal women. By binding to the ER in hormone-sensitive breasts, TAM acts as an estrogen antagonist and interferes with the function of ERs and ultimately prevents the activation of genes by estrogen [78]. There are no reports about the teratogenicity of TAM in humans to this date. It is better not to use TAM as a treatment if the patient is pregnant. Even though the estrogen-like qualities of TAM can be beneficial for postmenopausal women in which the circulation of cholesterol decreases, it can develop endometrial carcinoma and encourage clones of BC cells to grow in response to the drug [79]. Studies have shown that about 30%–50% of patients with TAM therapy relapse or die. This can be explained by tumor-dependent ER activation, downstream pathways, and, most importantly, intrinsic host factors [80].

4.1. TAM Resistance. One of the main problems related to the remedy of BC is the development of resistance to TAM. Considering the valuable effects of TAM, it is clear that overcoming and preventing TAM resistance are a significant clinical goal. The mechanisms of TAM resistance depend on many factors, such as the inactivation of antioncogenes, the activation of oncogenes, changes in the expression of ER, and the influence of growth factor signal pathways; however, the suppress of ER alpha (ER α) is a significant mechanism when it comes to TAM resistance [81, 82]. Antiestrogen resistance can be categorized into two groups: de novo resistance and acquired resistance. De novo resistance refers to the BC cells being nonresponsive to antiestrogen therapy from the beginning of the treatment. This type of resistance is observed in the ER^+ human BC cell line that is transfected with the HER2/neu gene, which induces cancer growth. On the other hand, acquired resistance occurs after long-term therapy in ER^+ BC that initially responded to antiestrogen therapy [79].

TAM resistance in BC classified two nongenetic and genetic mechanisms.

Nongenetic mechanisms usually occur during or after treatment due to environmental adaptation and various causes. These causes include the following:

Epigenetic changes: epigenetic changes, including DNA methylation, can cause the silencing of some genes [83].

Noncoding RNAs: some long noncoding RNAs (lncRNA) and microRNAs (miRNAs) can cause resistance to TAM [17].

Activation of autophagy: one of the mechanisms of cancer cells in drug resistance, including TAM, is the activation of the autophagy pathway and increased drug resistance [84].

Other mechanisms of cancer cells in resistance to TAM include the conditions of the tumor microenvironment and the cells in the tumor microenvironment (TME) and the diversity of drug metabolism [85].

Loss of ER expression: the therapeutic effect of TAM derives from mediating ER signaling, and the degree of ER expression is a great predictor of response to TAM; therefore, the loss of ER is attributed to TAM resistance. The lack of ER expression is known to be the dominant mechanism for de novo TAM resistance. The loss of ER expression results in an initial switch from ER^+ to ER-negative phenotype. The mechanisms that cause the loss of ER expression are (1) transcriptional repression of the ER gene and (2) population remodeling, which leads to the overpopulation of ER-negative cells. It is evident that miRNAs are the critical regulators of many processes and diseases in the body. They work as post-transcriptional regulators by targeting mRNAs and regulating cellular processes such as differentiation, growth, and apoptosis [85–87]. It has been proven that about 50% of ER^+ BCs are resistant to endocrine therapy, and 30%–40% of those reactive to TAM will become resistant to TAM. Interestingly, TAM has a protective effect on women with BRCA1 or BRCA2 mutations, and it diminishes the risk of contralateral BC in women with BC and BRCA1 or BRCA2 mutations [40].

Endocrine adaptation: elevated steroidal levels in postmenopausal women could limit the ER saturation by TAM and, therefore, cause resistance. Meanwhile, this mechanism is not related to the acquired type of TAM resistance and is not likely to be the leading cause of resistance [86]. Genetic resistance to TAM in BC is also inherent in the individual and can be attributed to various factors, including activation of the PI3K/AKT/mTOR pathway, increased HER2 expression, changes in coregulators, and mutations in ER.

4.2. Methods to Overcome TAM Resistance. One approach to treating cancer is to target cell-cycle proteins other than SERMs, such as CDK-4/6 and histone deacetylase inhibitors, in combination with TAM. Another method is to target the AKT pathway using histone deacetylase inhibitors, which promote cell proliferation. The AKT pathway may be elevated, allowing cancer cells to use ER in the presence of TAM [88]. ASA reduces drug resistance by blocking the G0/G1 phase-resistant cells and inhibits the phosphorylation of AKT, which can reduce resistance in cancer cells. Aspirin also inhibits the NF-KB activation, which overcomes the drug resistance. Other than aspirin, proteasome inhibitors

(PIs) combined with TAM are proven to be beneficial [82]. Another strategy is to use new generation SERMs to inhibit ER signaling pathways such as idoxifene, toremifene, and droloxifine and ring fixed compounds such as raloxifene, arzoxifene, and, EM-800. The new generation has greater binding affinity for ER and reduced agonist activity in contrast to TAM. TAM can reduce the production of VEGF in estrogen-dependent cells. Meanwhile, in TAM-resistant cells, the vascular endothelial growth factor (VEGF)/VEGF receptor 2 (VEGFR2) signaling remains active. Thus, the usage of VEGF inhibitors and VEGFR2 antagonists can help treat BC [89].

5. Conclusion

BC, which is a great limitation for women in the society, must be identified and detected. Among the important risk factors for BC, we can mention the genes whose mutation or disruption play a significant role in the spread and occurrence of BC. There are different methods for treating BC, which include surgery and chemotherapy. One of the most important drugs used to treat BC is TAM. Various factors cause resistance to TAM. One of the factors of resistance to TAM is the genes mentioned above, so mutations in these genes can lead to resistance to TAM; however, one of the strategies of BC treatment is to identify the genes involved in TAM resistance. Therefore, more studies are needed in the future to reveal the exact role of genes involved in TAM resistance.

Data Availability Statement

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Ethics Statement

This article does not contain any studies with human participants or animals performed by any of the authors.

Conflicts of Interest

The authors declare no conflicts of interest.

Author Contributions

Elmira Aboutalebi Vand Beilankouhi, Yosra Vaez-Gharamaleki, Reza Zarezadeh, and Peyman Hassani were involved in writing the article. Mohammad Rasoul Amini was involved in drawing figure. Mohammad Valilo, Reza Safaralizadeh, and Elmira Aboutalebi Vand Beilankouhi participated in the study design and reviewing.

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