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Breast cancer in the geriatric population – risk factors and prevention strategies

Rak piersi w populacji geriatrycznej – czynniki ryzyka i strategie zapobiegania

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Abstract

Breast cancer, most commonly diagnosed in women over 60, represents a substantial challenge for the health system. This review examines key risk factors, distinguishing between non-modifiable elements (age, genetics, reproductive history) and modifiable elements (postmenopausal hormone therapy, obesity, lifestyle). We examine the importance of genetic screening, which involves tests like BRCA1, BRCA2, and multigene panels. Although these tools are powerful, they come with challenges including false positives, overdiagnosis, and privacy issues. Prevention of breast cancer can be separated into primary and secondary measures. Primary prevention includes weight management, dietary changes, moderate alcohol consumption, and physical activity. Secondary prevention involves routine screening through mammography, self-breast examination, clinical breast examination, and in selected cases, ultrasound and magnetic resonance imaging. This review seeks to guide health providers towards appropriate breast cancer preventive strategies and screening measures, improving overall health outcomes in the geriatric population. (Gerontol Pol 2023; 31; 250-257) doi: 10.53139/GP.20233130

Keywords: *geriatric breast cancer, menopause and breast cancer, BRCA1 and BRCA2 in older women*

Streszczenie

Rak piersi jest najczęściej występującym nowotworem wśród kobiet. Każdego roku na całym świecie diagnozowany jest u ponad 1,5 miliona kobiet. Szacuje się, że do 2050 roku zapadalność na raka piersi może osiągnąć poziom nawet 3,2 miliona przypadków rocznie. Prawie jedna na osiem kobiet zachoruje na raka piersi w ciągu swojego życia. Rak piersi zdecydowanie częściej dotyka kobiet starszych. Prawdopodobnie jest to spowodowane aspektami związanymi ze starzeniem się takimi jak wielochorobowość, polipragmazja i niepełnosprawność, które mogą niekorzystnie wpływać na etap diagnozowania, progresję raka oraz rokowanie. Do czynników negatywnie wpływających na rokowanie u starszych pacjentek zaliczamy między innymi: wiek, ekspozycję na promieniowanie jonizujące oraz hormonalną terapię zastępczą po menopauzie. W efekcie śmiertelność z powodu raka piersi u pacjentek starszych jest wyższa (59% u kobiet w wieku ≥65 lat) niż wśród pacjentek młodszych (41% u kobiet w wieku <65 lat). W diagnostyce raka piersi dużą rolę odgrywają metody takie jak: samobadanie, badanie fizykalne przez lekarza oraz przesiewowe badania obrazowe piersi, takie jak USG, mammografia i rezonans magnetyczny. Ostateczne rozpoznanie stawia się na podstawie biopsji cienkoigłowej lub gruboigłowej i badania histopatologicznego. Pozwala to na szczegółową ocenę typu guza, stopnia zaawansowania, hormonozależności, nadekspresji HER2 oraz wskaźnika proliferacji Ki67. Metody te pozwalają na indywidualne podejście do leczenia raka piersi, które może obejmować interwencje chirurgiczne, chemioterapię, radioterapię i terapię hormonalną. W krajach rozwiniętych, w wyniku skutecznej profilaktyki i strategii diagnostycznych, 5-letnie przeżycie raka piersi zbliża się obecnie do 80%. Celem naszej pracy jest przedstawienie czynników ryzyka raka piersi oraz aktualnie wykorzystywanych metod zapobiegania chorobie w kontekście pacjentów geriatrycznych. (Gerontol Pol 2023; 31; 250-257) doi: 10.53139/GP.20233130

Słowa kluczowe: *rak piersi u osób starszych, menopauza a rak piersi, BRCA1 i BRCA2 u starszych kobiet*

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Introduction

Breast cancer continues to be the most common cancer in women [1]. Globally, over 1.5 million women receive a diagnosis for this condition each year [2]. By 2050, up to 3.2 million cases may be reported on an annual basis [3]. Nearly one in every eight women will develop breast cancer during their lifetime [4].

Elderly women are disproportionately affected by breast cancer. This is likely due to the unique characteristics of elderly populations, such as multimorbidity, polypharmacy, and disability, that can adversely affect stage of diagnosis, cancer progression and treatment outcomes. Factors that lead to increase in negative outcomes for elderly patients with breast cancer include age, exposure to ionizing radiation, and postmenopausal hormone replacement therapy among others. As such, the mortality through breast cancer among older adults is higher (59% in women ≥65 years old) than the mortality among younger adult patients (41% in women <65 years old) [5].

Diagnosis of breast cancer often involves self-examination, physical examination by a healthcare provider, and breast imaging screening such as ultrasound, mammography, and magnetic resonance imaging. A definitive diagnosis is made through fine or core needle biopsy and histopathological examination. This allows for detailed assessment of tumor type, stage, hormone-dependence, HER2 overexpression, and Ki67 proliferation index [6].

These methods contribute to a personalized approach to breast cancer treatment, which may encompass surgical interventions, chemotherapy, radiation therapy, and hormone therapy [7]. In developed nations, as a result of effective prevention and diagnostic strategies, the five-year survival rate for breast cancer now approaches 80% [2]

We aim to provide an overview of breast cancer risk factors within the context of geriatric patients. In addition, we explore current prevention strategies especially those relevant to older adults.

Non-Modifiable Risk Factors

Age

Age is the most significant risk of breast cancer among women, with most patients diagnosed at the age of 50 or more [4].

Family history and genetic Factors

Breast cancer has been linked to family history in 25% of cases [8]. A study in the UK of more than 113,000 women demonstrated that the risk of breast cancer is 75% higher in women with first-degree relatives with the disease. The risk increases almost 100% when two or more relatives are diagnosed with breast cancer [8].

Oncogenes and their role in breast cancer

Oncogenes are central to understanding the development and progression of breast cancer. Oncogenes may influence the transition of a healthy cell to a cancerous cell, by virtue of mutation or altered expression. The most significant oncogenes in the context of breast cancer are HER2, EGFR, and c-Myc.

HER2 (Human Epidermal Growth Factor Receptor 2): The HER2 gene (c-erbB-2), located on chromosome 17q12, controls key aspects of cell growth and development. The amplification or overexpression of this gene is observed in approximately 20% of breast cancer cases and can precipitate an aggressive tumor growth pattern [2]. This amplification process may result in increased levels of HER2 gene copies in breast cancer cells, enhancing HER2 protein production. This in turn leads to rapid cell division and tumor proliferation. With the advent of targeted therapies that focus specifically on the HER2 gene, there has been significant progress in terms of improved patient breast cancer outcomes [2].

EGFR (Epidermal Growth Factor Receptor): The EGFR gene, located on the short arm of chromosome 7 (7p12), encodes a cell-surface protein integral to cell growth and division. In the context of inflammatory breast cancer (IBC), an aggressive subtype of breast cancer, EGFR is overexpressed in more than 30% of cases. This overexpression can drive cancer cell growth, hastening disease progression and generally leading to worse patient outcomes. However, like HER2, EGFR is also susceptible to targeted therapies, offering more individualized treatment strategies and the potential for enhanced patient outcomes [9,10].

c-Myc: The c-Myc gene, situated on the long arm of chromosome 8 (8q24), encodes the Myc protein, a transcription factor responsible for transcribing genetic information from DNA to mRNA. Myc, modulate the expression of a vast array of genes. Playing a regulatory role in nearly 15% of all genes, the Myc protein is central to processes like cell cycle progression, programmed cell death (apoptosis), and cellular transformation. Overexpression of c-Myc can lead to uncontrolled cell growth. Myc controlled genes such as MTA1, hTERT, and PEG10, have been associated with breast cancer.

The overexpression of c-Myc is predominantly observed in highly malignant breast cancers, contributing to their aggressive phenotype [11,12]. While therapeutic targeting of c-Myc presents a challenge due its involvement in basic cellular functions, ongoing research aims to inhibit its cancer-promoting activity, potentially opening new avenues for breast cancer treatment.

Tumor suppressor genes and their role in breast cancer

Tumor suppressor genes, also known as antioncogenes, play a critical role in controlling cell growth and preventing the development of cancer. When these genes are altered or mutated, they can no longer perform their protective role, leading potentially to cell growth that is uncontrolled and the development of cancer.

TP53: Mutations to this gene, which is involved in cell cycle regulation and apoptosis, leads to Li-Fraumeni syndrome (LFS), a rare hereditary condition that predisposes to early-onset tumors, including breast cancer. Women with LFS have an increased risk of developing breast cancer pre-menopause, with 64-83% of these tumors being HER2-positive, suggesting a distinct molecular subtype within this group [13].

STK11 (LKB11): Mutations to the STK11 gene, which encodes a serine-threonine kinase involved in cell polarity and energy metabolism, are commonly associated with Peutz-Jeghers syndrome (PJS) [14]. Individuals with PJS face an elevated risk of gastrointestinal cancers, as well as breast and ovarian cancers. The cumulative risk of breast cancer with PJS is around 32-54%, indicating a substantial contribution to the overall cancer burden in these patients [15,16].

PTEN: This gene regulates cell division and mutations are associated with Cowden syndrome. Cowden syndrome is characterized by a significantly increased risk of developing breast cancer, with a lifetime risk estimated at 85 percent [17,18].

PALB2: The PALB2 gene codes for a protein that interacts with the product of the BRCA2 gene to repair DNA damage in a process known as homologous recombination. This interaction maintains genetic stability and prevents deleterious mutations [19]. By the age of 80 years, up to 53% of individuals with this mutation may develop breast cancer. Interestingly, cohort studies among carriers of the mutated PALB2 gene show a stronger association with estrogen receptor-negative breast cancers [20]. The PALB2 gene is also associated with pancreatic cancer.

CDH1: The CDH1 gene encodes for E-cadherin, a protein involved in cell adhesion. Mutations to CDH1 are primarily associated with hereditary diffuse gastric cancer, but they also contribute to lobular breast cancer. Notably, breast cancers associated with CDH1 mutations often develop before the age of 40, which requires early screening in patients with these mutations [21].

Breast Density

Breast tissue density is determined by the ratio of connective and glandular tissue to fatty tissue. Dense breasts, where more than 75% of the tissue is composed of dense glandular and connective tissue, are associated with the development of breast cancer. However, high breast tissue density has not been associated with any specific type of breast cancer. In addition, high breast density has not been associated with increased mortality in patients with breast cancer [13].

Reproductive Factors

Reproductive history is a factor in breast cancer risk. This includes early menarche, late menopause, and older age at first pregnancy. For every year that menopause is delayed, the risk of developing breast cancer increases by approximately 3%. Similarly, each year that menarche is delayed or for each additional childbirth, the risk of developing breast cancer is reduced by between 5% to 10% [22-24]. A study from Norway found that women who had their first child after the age of 35 faced a 54% greater risk of developing breast cancer compared to women who gave birth before their twenties [25]. This information underscores the intricate relationship between a woman's reproductive history and her risk of developing breast cancer, suggesting potential avenues for preventative strategies.

Modifiable Risk Factors in the Geriatric Population

Lifestyle Choices

Diet, physical activity, alcohol consumption, are significant for the overall health of the elderly, including their risk of developing breast cancer.

Diet: A diet high in fat, particularly saturated fat, significantly worsens prognosis and increases mortality (RR=1.3) [26]. Conversely, a well-balanced diet, rich in fruits, vegetables, lean proteins, and whole grains, can contribute to overall health and possibly decrease the risk of breast cancer in older individuals. It's also crucial to limit the intake of processed and red meats, which have been linked to an increased risk of breast cancer.

Physical Activity: Even moderate exercise can be beneficial for the elderly, contributing to lower breast cancer risk. Tailored, low-impact activities, like walking, swimming, or chair exercises, can help elderly individuals achieve recommended physical activity levels without causing stress on joints and muscles [27].

Alcohol Consumption: Excessive alcohol consumption may increase the risk of breast cancer by affecting estrogen levels, the number and sensitivity of estrogen receptors, and the presence of alcohol metabolism products. A meta-analysis based on 53 epidemiological studies suggests that consuming 35-44 grams of alcohol daily can raise the risk of breast cancer by 32%, with a 7.1% increase for every additional 10 grams of alcohol consumed per day [28,29]. Breast cancer is the most common cancer associated with alcohol consumption.

Smoking: Although the link between smoking and breast cancer remains controversial, it is currently believed that smoking increases the risk of breast cancer [30].

Obesity and Postmenopausal Hormone Therapy

Obesity may increase the risk of breast cancer. This is particularly true for women after menopause, as excess fat tissue can lead to increased estrogen levels, stimulating the growth of breast cancer cells. Mechanisms linking to breast cancer to obesity include insulin resistance, increased production of insulin-like growth factors (IGF), alterations in sex hormone metabolism, chronic inflammation, changes in adipocytokine and endothelial growth factor (VEGF) production, alterations in immune response, and oxidative stress [31]. According to The Million Women Study, conducted with over 1.2 million women in the UK, the risk of postmenopausal breast cancer is 30% higher in cases of obesity [32].

Postmenopausal hormone therapy, which some women may use to manage menopausal symptoms, can increase breast cancer risk, particularly with long-term use. Both endogenous estrogen, usually produced by the ovaries in premenopausal women, and exogenous estrogen, primarily sourced from oral contraceptives and hormone replacement therapy (HRT), are associated with increased breast cancer risk [2]. The Million Women Study in the UK determined that the risk of breast cancer in women using HRT was 66% higher compared to those who did not use it [33]. The risk significantly decreases two years after discontinuing HRT [34].

Late menopause, which extends the time of exposure to estrogen, is associated with an increased risk of breast cancer. Although this isn't a factor that can be directly modified, understanding this relationship is crucial in managing breast cancer risk in older women.

Genetic Screening for Breast Cancer

Genetic screening is an essential tool in the fight against breast cancer. Screening can be particularly beneficial for individuals with a family history of breast cancer or related cancers and those of specific ethnic backgrounds (such as Ashkenazi Jewish descent), or those who have certain genetic markers [35].

In addition to specific gene screening, such as BRCA1 and BRCA2, multigene panels, test for mutations in multiple genes simultaneously. Besides BRCA1 and BRCA2, these include genes such as PALB2, PTEN, and TP53, among others. Multigene testing provides a comprehensive assessment of an individual's genetic risk [36].

In addition to testing for high-penetrance genes, genomic risk stratification can be used to evaluate common minor genetic variants that cumulatively may contribute to increased breast cancer risk. This approach, known as polygenic risk scoring, can help to identify individuals at an elevated risk even in the absence of known high-risk mutations. [37]

Genetic counseling is an essential part of the genetic testing process. A genetic counselor can explain the potential benefits, limitations, and implications of genetic testing to help individuals make informed decisions. They can also provide support in understanding and managing the emotional aspects of genetic risk. In addition, individuals must understand that a negative genetic test does not eliminate the risk of breast cancer as most breast cancers are not due to hereditary factors, but rather a combination of environmental and lifestyle factors, in conjunction with aging and personal health history [38].

Disadvantages of Breast Cancer Screening

Breast cancer screening tools must be applied judiciously as there are potential drawbacks to universal screening, especially in people without significant family histories or other breast cancer risk factors.

False positives are a characteristic of most screening processes and may result in subjecting tested individuals to unnecessary stress, necessitate invasive testing, and potentially invasive procedures. Such outcomes may result in mental and physical harm

In addition, unjustified screening may lead to overdiagnosis and overtreatment if slow-growing or non-malignant cancers are detected. Such findings might otherwise have never resulted in any morbidity had they been left alone. Universal screening can be expensive and the rate of detection may not be cost-effective. [37] Shared, limited resources may be better invested in addressing higher-risk disease and populations as well as health

promotion endeavors. In terms of genetic testing, there exist concerns about privacy and potential discrimination based on genetic information. Finally, certain radiological exams, such as mammograms, may result in subjecting individuals to unnecessary radiation exposure.

Primary prevention

Primary prevention involves preventing disease by limiting exposure to risk factors or increasing individual immunity. Primary prevention in breast cancer includes: weight loss for overweight individuals, reducing fat consumption, limiting alcohol consumption, and increasing physical activity, especially in postmenopausal women.

Weight loss was shown to reduce the risk of breast cancer in a meta-analysis of prospective and retrospective studies, including approximately 237,000 cases and 4 million participants [27]. The Women's Health Initiative conducted research on 61,000 postmenopausal women, women who reduced their body weight by more than 5% within three years of the study's start had a lower incidence of breast cancer for an average of 11.4 years compared to women whose weight did not change [39].

According to a study conducted on over 48,000 postmenopausal women, reducing the amount of fat consumed correlates with a decrease in mortality due to breast cancer [39]. In the prospective Women's Health Study during an average 10-year observation, even moderate alcohol consumption increases the risk of breast cancer [40]. A meta-analysis of 139 prospective and retrospective studies, covering over 4 million participants, showed that physically active women have lower risk of developing breast cancer (OR 0.78, 95% CI 0.76-0.81) than physically inactive women. The results were similar for both pre- and post-menopausal women and for light and high intensity physical activity [27]. The reduced risk of disease is likely due to hormonal changes associated with physical exertion such as reduced plasma estrogen concentrations, insulin, and insulin-like growth factor 1 [41].

Secondary prevention

According to the 2019 guidelines of the American College of Physicians, mammography should be performed every 2 years in women with an average risk of breast cancer aged 50-74 years. Preventive mammography should not be used in women with an expected survival time of less than 10 years and those who have reached 75 years or more. It can be considered in women with an average risk of breast cancer aged 40-49 years, but each case should be assessed individually, considering potential benefits and harms [42]. In Poland, the Population Program for Early Detection of Breast Cancer operates as part of secondary prevention of breast cancer, which involves providing women aged 50-69 with a free mammography examination. The examination can be performed once every two years [43].

Self-breast self examination is a non-invasive method of secondary prevention and includes visual inspection and palpation of the breast. The patient should pay attention to any changes in the shape and size of the breast, enlargement of the surrounding lymph nodes, the presence of lumps and nipple discharge [44]. The American College of Obstetricians and Gynecologists (ACOG) and the American Medical Association recommend monthly breast self-examination and suggest that women should know their physiology to be able to detect any abnormalities earlier [45]. Unfortunately, breast self-examination has low sensitivity and specificity and there is no improvement in mortality rates associated with this screening measure [46].

Clinical breast examination. Clinical breast examination includes an interview, physical examination and palpation of the breasts and lymph nodes by a doctor. This examination can assess lumps and skin changes in the breasts and detect changes missed during routine screening mammography. So far, no clinical trials have been conducted assessing the effectiveness and sensitivity of clinical examination alone. There is evidence, however, that clinical breast examination in combination with mammography increases the sensitivity of screening [46]. According to ACOG recommendations, clinical breast examination should be performed once every 1-3 years in women aged 20-39 years and once a year in women aged 40 years and older [45].

Ultrasound screening can be helpful in early detection of breast cancer recommended for women aged 20-40 years. Due to changes in breast tissue associated with aging, ultrasound is less effective in patients above 40 years of age. According to the Polish Oncology Union, breast USG should be performed once a year or earlier if lumps, nipple discharge or skin retraction are detected [44].

Magnetic resonance imaging. Magnetic resonance imaging is useful in imaging breasts in which changes may be invisible in mammography and USG. It allows for precise imaging of the entire breast in all planes, but it is not routinely used in secondary prevention due to the high cost of the examination and a large number of false positive diagnoses caused by difficulties in distinguishing benign from malignant changes [46,47].

Summary

Breast cancer is the most common cancer among women, with every second patient being aged 60+ years. While incidence of breast cancer is increasing, meticulous primary and secondary prevention strategies significantly reduce morbidity and mortality associated with the disease. Patient education plays a fundamental role in improving breast cancer outcomes, enabling a reduction of modifiable risk factors through health-promoting interventions.

Conflict of interest
None

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