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CURRENT VIEW ON THE EPIDEMIOLOGY OF BREAST CANCER: A LITERATURE REVIEW

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ABSTRACT

Relevance: *Breast cancer (BC) is the leading cause of worldwide female cancer mortality. The constant development of treatment strategies and diagnostic tools has increased the survival rate for BC. Next-generation genome sequencing (NGS) identifies the genetic changes responsible for tumor emergence, development, and metastasis. NGS has expanded the capacities of BC diagnostics, treatment, and early prevention in women.*

The study aimed to *identify breast cancer risk factors in women.*

Methods: *Publications were obtained from the following databases: PubMed, Google Scholar, and eLibrary. The depth of the search was 5 to 10 years. As a result, 100 literary sources were identified, of which 26 publications formed the scientific material for this review.*

Results: *Breast cancer is a heterogeneous disease driven by genetic abnormalities and epigenetic alterations.*

Conclusion: *Gene mutations do not change. Genetic testing shall be introduced as a preventive measure to reduce BC incidence. Lifestyle-related BC risk factors can be addressed to minimize BC risk.*

Keywords: *breast cancer, epidemiology, risk factors, prevention.*

Introduction: Breast cancer (BC) is an urgent medical and social problem. Risk factors that initiate malignant transformation can be divided into two groups. The first group includes elements not amenable to change. These are independent parameters that do not change throughout a lifetime. The second group is risk factors whose influence on the tumor process can be altered [1].

In 2020, more than 2.2 million BC cases were registered worldwide, and approximately 685,000 women died from this disease [2]. According to Globocan, in 2020, BC became the most common cancer in women globally (157 countries) (Figure 1) [3].

In 2020, 4307 new BC cases were registered in the Republic of Kazakhstan (RK). BC ranked first in the female cancer incidence structure, with a share of 25.8% (vs. 27.2% in 2019). BC also led the cancer incidence structure in both sexes, accounting for 14.5% (vs. 15.2% in 2019). In cancer mortality structure, BC ranked third for eleven years in a row, with a share of 7.8% in 2020 (vs. 8.1% in 2019) [4].

The study aimed to identify the studied and new risk factors and determine the causes of BC in women.

Materials and methods: The authors searched the PubMed database, Google Scholar, and eLibrary electronic libraries. The following keywords were used to search for information: "breast cancer," "epidemiology," "risk factors," "prevention," and "genomic sequencing." As a result, 100 literary sources were identified, of which 26 publications met the criteria and became the basis of the academic review.

Inclusion criteria: reviews, meta-analyses, and articles on the epidemiology of BC over the past decade.

Publications more than ten years old or not meeting the main purpose of this review, or describing animal studies, were excluded from the review.

Results:

BC risk factors that cannot be altered (gender, age, genetic mutations, menarche).

Currently, risk factors are split into changeable and unchangeable ones. The female gender is attributed to fundamental risk factors [5].

The risk of developing BC increases with age. BC is often diagnosed at 55 to 64 years [6]. The average age of BC diagnosis in China (50-54 years) is lower than in the US and EU (55-59 years) [7].

The new-generation genome sequencing helps determine the gene mutation spectrum, assess the risk of diseases, and develop a personalized approach to treatment [8]. The mutations in the Breast cancer 1 (BRCA1) and Breast cancer 2 (BRCA2), Tumor Protein p53 (TP53), Phosphatase and tensin homolog deleted on chromosome 10 (PTEN), Cadherin 1(CDH1), Serine/threonine kinase 11 (STK11) were found to be associated with a high risk of BC. Moderate risk genes involved in neoplastic transformation include Ataxia telangiectasia mutated (ATM), Checkpoint kinase 2 (CHEK2), and Partner and localizer of BRCA2 (PALB2) [9].

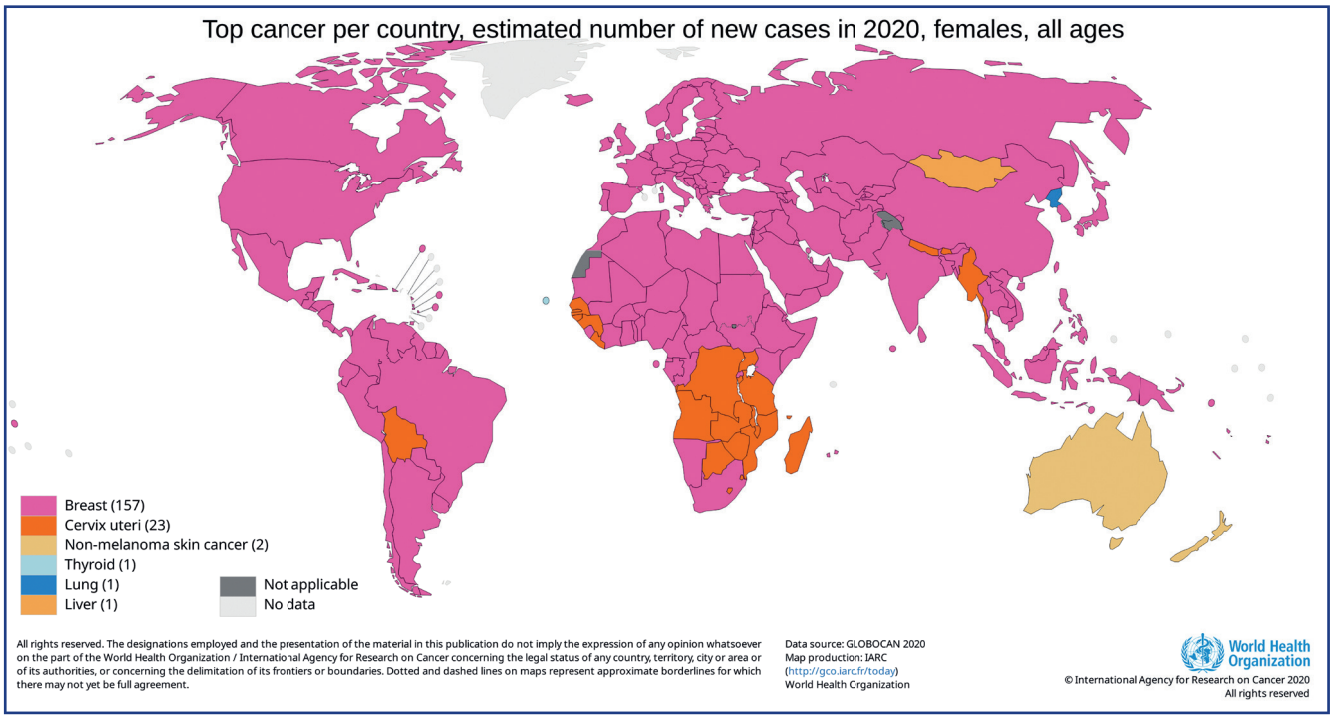

Figure 1 – Leading malignant neoplasms by country, standardized by age, incidence rates (World) in 2020, both sexes, all ages (except skin cancer) [3]

Women with early menarche are at an increased risk of BC, probably due to earlier ovulation and the resulting longer exposure to estrogens. A case-control population study of reproductive risk factors for various subtypes of BC in women aged 20 to 44 did not reveal any statistically significant relationship between the age of menarche and any BC subtype [10].

Risk factors that can be altered (parity, benign breast diseases, overweight, alcohol, smoking, implant installation, taking contraceptives, and diet)

The Chinese Society of Breast Surgery merges mastopathy, fibroadenomas, fibrocystic mastopathy, mastalgia, fibrocystic changes, and benign breast dysplasia under the "breast hyperplasia" term. In their practice guideline, Fibrocystic mastopathy is associated with a 1-5% risk of malignant degeneration, and morphologically-verified fibrocystic mastopathy with atypical ductal hyperplasia is associated with a high risk of BC [11].

Late menopause and no history of labor belong to high BC risk factors. Higher parity (pario (Lat.)— a history of labor or the number of previous labors) and lactation are associated with a lower BC risk [12].

Obesity and its association with BC rely on complex molecular mechanisms. In obese people, the adipose tissue creates an environment for cancer invasion and metastasis; biological agents in adipose tissue increase inflammation, suppress antitumor immunity, and promote tumor angiogenesis, growth, and metastasis [13].

In the updated version of the World Cancer Research Fund and the American Institute for Cancer Research (WCRF/AICR) 2018 report involving 16 prospective studies of BC in premenopausal and 34 in the postmenopausal period, alcohol consumption is called a "probable cause" and "a convincing cause" of premenopausal and postmenopausal BC [14].

Increased breast density on mammography is a high-risk factor for BC. In a study conducted in Germany, Japan, Sweden, and the US, alcohol consumption was associated with an increased risk of high-density breasts [14].

In 2009, the Canadian expert panel on tobacco smoke and BC risk conducted an extensive review of 22 cohort data published before 2012 and 27 case-control reports published from 2000 to 2011. They found a 10%-higher risk of BC in persistent smoking [15].

Oral contraceptives are also associated with a risk of BC. A population-based case-control study conducted in 2004-2010 among 985 women with BC and 882 controls revealed a 50% higher risk of BC after taking oral contraceptives for more than 15 years (compared with never use). However, a shorter intake of oral contraceptives was not associated with a risk of BC [16].

An observational case-control study conducted in two groups from 1998 to 2018 aimed to determine hormone replacement therapy as a risk factor for BC. The control group included 98,611 women with a primary BC diagnosis aged 50-79. The study group included 457,498 participants. The results showed a higher risk of BC in both estrogen and estrogen-progestogen consumers – by 17% and 60% during 1 to 4 years of intake and by 33% and 108% after 5 to 14 years of intake [17].

In the cohort study performed at Samsung medical center (Seoul, South Korea), textured breast implants for breast reconstruction were associated with BC recurrence risk. The study involved 650 patients (687 BC cases) with an average age of 43.5 years. Smooth implants were installed in 274 cases (39.9%), and textured implants – in 413 cases (60.1%) [18].

Several BC risk assessment tools have been developed, such as The National Cancer Institute's BC risk assessment tool, known as the Gale Model (https://bcrisktool.cancer.gov/), Breast cancer surveillance consortium risk calculator (https://tools.bcsc-scc. org/BC-5yearRisk/), an IBIS Breast cancer risk assessment tool (http://www.ems-trials.org/riskevaluator/), analysis of breast and ovaries incidence and an algorithm for assessing the carrier https://ccge.medschl.cam.ac.uk/boadicea/). The model choice and the interpretation of the results should be discussed with a geneticist [19].

Preventive measures to reduce the incidence of BC

Mammographic screening supports the early detection of BC and mammary gland benign tumors. 95-100% of patients who start treatment at stage I of the disease survive over five years. Preventive bilateral mastectomy reduces BC risk by about 90% and increases survival, especially in BRCA1 mutation carriers [20].

A meta-analysis by G.U. Eleje et al. covered 10 cohort studies involving 8087 carriers of BRCA1 or BRCA2 mutations, including 2936 (36%) after surgery and 5151 (64%) controls. The median follow-up was 0.5 to 27.4 years. The study suggested that bilateral salpingo-oophorectomy in women with BRCA1 or BRCA2 mutations improves overall survival and reduces deaths from serous fallopian tube cancer (SFTC) and BC in women with mutations in both genes. Bilateral salpingo-oophorectomy could also reduce the risk of death from SFTC and BC in women with BRCA1 mutations. Still, it is not clear whether the risk decreases in BRCA2 mutation carriers [21].

According to the WHO recommendations, moderate-intensity physical activity lasting up to 2.5 hours per week reduces the risk of BC in healthy women by 12% (HR=0.88; 95% CI 0.84-0.91) [22].

An expert report published by the World cancer research foundation (WCRF) recommends limiting fast food and sugar-containing products. Plant foods and whole grain products could support cancer prevention due to their antioxidant, anti-inflammatory, and antitumor effects [23].

Saturated fats and red and processed meat increase circulating endogenous estrogens, insulin-like growth factors, and pro-inflammatory cytokines, thereby contributing to BC development. Polyunsaturated fatty acids, vitamins C and E, and fresh fruits and vegetables reduce the risk of BC occurrence and recurrence [24].

BC is a disease with genetic and epigenetic components. Genome instability leads to mutations, copy number variations, and genetic rearrangements. Epigenetic mechanisms in BC include DNA methylation, histone modifications, and microRNA expression [25].

There is scientific evidence that epigenetic mechanisms are flexible genomic parameters influenced by diet, physical activity, tobacco smoking, alcohol consumption, psychological stress, night shift work, environmental factors, and drug therapy [26]. Epigenetic mechanisms can alter gene activity in response to lifestyle and environmental factors [27].

Discussion: Mammographic screening plays a vital role in fighting BC, which is carried out to diagnose benign and malignant neoplasms of the mammary glands at the stage when they can be cured.

Women with BC and BRCA gene mutations should discuss surgical prevention of ovarian cancer. Bilateral salpingo-oophorectomy is considered at 35-40 years in a BRCA1 mutation presence and 40-45 years with a BRCA2 gene mutation. A multidisciplinary team shall establish the need for bilateral preventive mastectomy and bilateral salpingo-oophorectomy, considering the age, marital status, and reproductive potential, since bilateral salpingo-oophorectomy has consequences in the form of early menopause, the risk of cardiovascular diseases developing while performing surgery before 35 years increases myocardial infarction risk by eight times [28].

Scientific data on genetic mutations that initiate BC development demonstrate the significance of genetic screening as a preventive measure for women. Some genetic mutations are expensive to diagnose. However, preventative measures can reduce BC incidence and mortality and, consequently, costs for treating this oncological pathology.

Conclusion: The analyzed literature proves the influence of gene mutations and external factors on BC. The theory that epigenetic mechanisms are amenable to change increases the probability of reducing morbidity by changing the lifestyle. Genetic mutations are not subject to change, but understanding the amenable factors is essential. Maintaining health implies regular physical activity, a healthy diet, avoiding alcohol and tobacco products, weight loss, annual preventive examinations, and implementing projects to raise awareness of the female population on preserving reproductive health.

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ТҰЖЫРЫМ

СҮТ БЕЗІ ОЫРЫНЫҢ ЭПИДЕМИОЛОГИЯСЫНА ҚАЗІРГІ КӨЗҚАРАС: ӘДЕБИ ШОЛУ

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Өзектілігі: *Сүт безі қатерлі ісігі бүкіл әлем бойынша әйелдер арасындағы қатерлі ісік өлімінің басты себебі болып табылады. Емдеу мен диагностиканың үнемі жетілдірілген стратегиялары сүт безі қатерлі ісігінің өмір сүру деңгейін арттырды. Келесі ұрпақ геномының*

реттілігі (NGS) ісіктің пайда болуы, дамуы және метастазында рөл атқаратын генетикалық өзгерістерді анықтайды. NGS қолдану әйелдерде осы ауруды диагностикалау, емдеу және алдын алу шараларын ертерек жүзеге асыру мүмкіндіктерін кеңейтті.

Зерттеудің мақсаты: *зерттелген және жаңа қауіп факторларын анықтау, сондай-ақ әйелдерде сүт безі қатерлі ісігінің себебін анықтау*

Әдістері: *Мақалалар келесі дереккөрлер арқылы зерттелді: PubMed, Google Scholar және eLibrary. Іздеу тереңдігі 5 жылдан 10 жылға дейін болды. Нәтижесінде 100 әдеби дереккөз анықталды, оның ішінде 26 басылым шолу мақаласының ғылыми материалына негіз болды.*

Нәтижелері: *Сүт безінің қатерлі ісігі – генетикалық және эпигенетикалық компоненттері бар гетерогенді ауру.*

Қорытынды: *Генетикалық мутациялар өзгерістерге ұшырамайды, олардың диагностикасы сүт безі қатерлі ісігімен сырқаттанушыларды азайту мақсатында профилактикалық шараларды енгізу мен қолдануды қамтиды. Сүт безі қатерлі ісігінің қаупін азайту үшін өмір сүру салтын қауіп факторларын өзгертуге болады.*

Түйінді сөздер: *сүт безі обыры, эпидемиологиясы, қауіп факторлары, алдын алу.*

АННОТАЦИЯ

СОВРЕМЕННЫЙ ВЗГЛЯД НА ЭПИДЕМИОЛОГИЮ РАКА МОЛОЧНОЙ ЖЕЛЕЗЫ: ОБЗОР ЛИТЕРАТУРЫ

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Актуальность: *Рак молочной железы (РМЖ) является основной причиной смерти от рака среди женщин во всем мире. Постоянно улучшающиеся стратегии лечения и диагностики позволили увеличить выживаемость при РМЖ. Секвенирование генома нового поколения (СНП) определяет генетические изменения, играющие роль в возникновении, развитии и метастазировании опухоли. Применение СНП расширило возможности диагностики, лечения и ранней профилактики РМЖ у женщин.*

Цель исследования *– выявление изученных и новых факторов риска, а также определение причин заболеваемости РМЖ у женщин.*

Методы: *Были изучены статьи, обнаруженные с использованием следующих баз: PubMed, Google Scholar и электронной библиотеке eLibrary. Глубина поиска составила от 5 до 10 лет. В результате были определены 100 литературных источников, из которых 26 публикаций явились основой для обзорной статьи.*

Результаты: *РМЖ – гетерогенное заболевание с генетическими и эпигенетическими компонентами.*

Заключение: *Генетические мутации не подвергаются изменениям, их диагностика предполагает внедрение и применение превентивных мер с целью снижения заболеваемости РМЖ. Факторы риска, обусловленные образом жизни, можно модифицировать и таким образом снизить риск появления РМЖ.*

Ключевые слова: *рак молочной железы, эпидемиология, факторы риска, профилактика, геномное секвенирование.*

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