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Overview of the epidemiology, risk factors, clinical features, diagnostics and prevention of breast cancer

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Abstract

Background. Breast cancer is an uncontrolled, malignant growth of the breast tissue, which generally occurs among middle-aged women. It became the most commonly diagnosed malignancy worldwide in 2020. Malignancy may lead to detrimental outcomes, therefore a proper insight into the risk factors, clinical manifestation, diagnostics, and prevention is crucial.

Aim. To analyze the literature presenting epidemiology, risk factors, clinical manifestation, diagnostic methods, and prevention of breast cancer.

Materials and methods. The search of the literature was conducted in PubMed and Google Scholar. Publications were selected using the following keywords: "Breast cancer", "Epidemiology", "Risk factors", "Clinical manifestation", "Diagnostics", "Prevention". A total of 33 articles published from 2013 to 2021 were reviewed.

Results. Breast cancer tends to occur in women older than 40 years and the occurrence increases with age. Well-established risk factors may be described as nonmodifiable, reproductive, and lifestyle-related. Malignancy is often asymptomatic in the early stages. The localized symptomatic lesion usually occurs as a palpable mass with skin changes. Axillary lymphadenopathy indicates that a locally spread disease is already present. Metastases mostly affect bones, brain, lungs, and liver, therefore symptoms may develop accordingly. Combined diagnostic consists of physical examination and imaging with the following ultrasound-guided core biopsy which is the gold standard for confirming a diagnosis. Prevention is based on the avoidance of risk factors or early detection by screening programs.

Conclusions. After analysis of the literature, epidemiology, well-established risk factors, symptoms, diagnostics, and prevention of breast cancer is presented.

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

1. Introduction

Breast cancer is a malignancy of the breast tissue which develop either in the lobules or in the ducts that connect the lobule to the nipple. The neoplastic process is described as noninvasive, if confined in the site where it developed, and invasive, if invades surrounding tissues [1]. The most common type of noninvasive breast cancer is ductal carcinoma in situ (DCIS), which accounts for approximately 90% of all cases [2]. Among invasive carcinomas, the most common is invasive ductal carcinoma (IDC), which accounts for approximately 75% of invasives lesions [3, 4]. The further progression of breast malignancy can lead to irreversible outcomes, therefore, the present review aims to provide an update on prevalence and mortality rates, and generally describe risk factors, symptoms, diagnostics, and prevention.

2. The aim

To analyze the latest scientific literature on epidemiology, well-established risk factors, clinical manifestation, fundamental diagnostic methods, and prevention of breast cancer.

3. Materials and methods

The search of publications was conducted in English in Pubmed and Google Scholar databases. Publications were selected using the following keywords: "Breast cancer", "Risk factors", "Epidemiology", "Symptoms", "Clinical manifestation", "Diagnostics", "Prevention", "Screening mammography". The selected period was from 2013 onward. In total were selected 33 articles. In this article is presented summarized analysis of scientific articles results.

4. Results

4.1. Epidemiology

Breast cancer is the most common malignancy among women with an expected continuous increase of occurrence and mortality [3]. In 2020, according to the World Health Organization (WHO) data, breast cancer surpassed lung cancer and became the world's most prevalent cancer. It has been estimated 2.3 million new cases and 685 000 deaths in 2020, and the incidence rate is predicted to reach 3.2 million by 2050 [3, 5]. In Lithuania, the number of cases and death rose over the past decade as well, and 18065 new cases (6,46 per 100 000 population) and 564 new deaths (20,2 per 100 000 population) have been recorded in 2020 [6, 7]. Geographically, the highest prevalence is in North America, Australia/New Zealand, and in Western and Northern Europe, and the lowest in Asia and sub-Saharan Africa [8].

4.2. Risk factors

Some risk factors appear to be associated with the development of breast cancer and they can be divided into several groups such as nonmodifiable, reproductive, and lifestyle factors [3].

Nonmodifiable risk factors include gender, age, genetics, family history, and race. Breast tissue malignancy predominantly occurs in women with an incidence rate of 99% and more, while in men it accounts for less than 1% [3, 9]. Many studies show, that the risk for breast tumor rises with increasing age [3, 8, 10, 11]. The risk begins to rise sharply after the age of 40 and reaches its peak in the age of menopause [3, 5, 11, 12]. It has been accounted, that around 5-10% of all breast cancer cases are due to genetic predisposition and most are associated with mutations in BRCA1 and BRCA2 genes.

Lifetime breast cancer risk ranges from 80% to 90% for *BRCA1* variant carriers and 60% to 85% for *BRCA2* variant carriers [5, 13, 14]. In regard to family history, a higher risk is associated with an increasing number of first-degree relatives diagnosed with breast malignancy before age 50 years. According to the studies conducted in the United States, white women have the highest breast cancer incidence overall, while black women have the highest incidence among women younger than 40 years [5, 15, 16].

In the background of reproductive risk factors of breast cancer, the key role belongs to the ovarian hormones which effect begins at the puberty age, continues during the monthly cycles, and ultimately decreases in menopause. In relation to these physiological reproductive hormones alterations, it has been established that early menarche, late menopause, late age at first pregnancy, and low parity increase the risk to develop for breast cancer. Younger age of the onset of menarche increases the risk by two times and each 1-year delay in menarche decreases the risk by 5% [3, 17]. The age of the onset of menopause is significant if is 50 years of age or older and each 1-year delay raises the risk of getting a breast tumor by 3% [3, 17, 18]. In regard to pregnancy, chances of malignant breast lesion occurrence rise in cases of the older age of first pregnancy or low parity [3, 19]. It is thought, that the risk increases if the first full-term pregnancy occurs in women older than 30 years while each additional birth decreases the risk by 10% [17, 19]. Additionally, hormonal therapy, which is an exogenous factor influencing reproductive system balance, is related to breast cancer development. The risk of oral menopausal hormone therapy depends on

agents and duration of use. Two-component therapy containing estrogen and progesterone enhances the risk while estrogen-only therapy is not associated with increased risk. Also, prolonged duration of therapy appears to be associated with breast malignancy while short-term use does not show significant influence [12, 20, 21].

Lifestyle risk factors refer to obesity, alcohol consumption, smoking. Obesity positively correlates with breast cancer due to higher rates of conversion of androgenic precursors to estrogen through peripheral aromatization in adipose tissue [3]. Obese postmenopausal women (BMI of 30 kg/m² or greater) are at increased risk, with a relative risk of about 1.3 compared to women with weight within the reference range (BMI less than 25 kg/m²) [22]. Alcohol showed to be a risk factor for hormone receptor-positive and hormone receptor-negative breast tumors. Active smoking, especially in postmenopausal women, and prenatal smoking, has also been associated with breast cancer [3].

4.3. Clinical features

Clinical manifestation of breast cancer occurs in relation to the stage of the disease. The early-stage primary tumor often does not cause prominent symptoms and it may lead to late detection. Localized symptomatic form occurs as a painless firm mass in a breast and usually is detected by a patient during self-examination. Additionally, skin changes such as erythema, tenderness, ulceration or dimpling, and nipple changes including nipple retraction or discharge, alterations of breast size or shape, may be observed. The locoregional disease manifests as axillary or supraclavicular lymphadenopathy in addition to localized breast

symptoms mentioned previously [2, 5, 14, 23]. The advanced stage of breast cancer may present with bones, brain, liver, and lungs symptoms as these organs are the most common sites of involvement. Metastases in the bone cause pain and swelling. CNS damage manifests as persistent and worsening headache, particularly while lying down, vision disturbances, nausea, vomiting, and seizures. Liver damage causes

jaundice, pruritus, anorexia, and abdominal pain. Respiratory system symptoms include dyspnea, chronic cough, and chest pain [14, 24].

4.4. Diagnostics

Comprehensive diagnostics of breast cancer is based on clinical examination in combination with imaging methods and confirmed by pathological assessment (Table 1).

Table 1. Diagnostic work-up for early breast cancer [25].

General status	Primary tumor	Regional lymph nodes	Metastatic disease
History	Physical examination	Physical examination	Physical examination
Menopausal status	Breast US	Lymph nodes US	Abdominal/pelvic CT or MRI (routinely not recommended)
Physical examination	Mammography	US-guided biopsy	Chest CT
Full blood count	Breast MRI		Bone scan
Liver/renal/cardiac function tests	US-guided biopsy		Liver tests
Alkaline phosphatase levels			Brain MRI
Calcium levels			

US – ultrasound; CT – computed tomography, MRI – magnetic resonance imaging

In any suspected breast cancer case, a general health status should be evaluated. Physical examination consists of bimanual palpation of the breasts and regional lymph nodes. If needed, the latter structures should be evaluated by imaging methods which include bilateral mammography and ultrasonography (US), and performed modality depends on the age of the patient [14, 25]. In women younger than 30 years ultrasonography is preferred, however, mammography is recommended in case of high suspicion for malignancy, while in women aged 30 years or older, mammography should be primarily performed [26]. An MRI of the breast

is not routinely recommended but should be considered in cases such as familial breast cancer associated with BRCA mutations or others [25]. However, for nonpalpable abnormalities, biopsy guided by mammography, ultrasonography, or MRI is a standard diagnostic method. It is important to emphasize, that patient in the absence of signs or symptoms suspicious for metastatic disease is not a subject to additional tests [27]. In terms of metastatic disease, additional testing depends on the stage of breast cancer. Abdominal and/or pelvic CT or MRI is required if a patient has elevated alkaline phosphatase level, abnormal results on liver

function tests, abdominal symptoms, or abnormal physical examination findings in the abdomen or pelvis. Chest CT is performed if pulmonary symptoms are present. The bone scan or sodium fluoride PET-CT should be done if localized bone pain or elevated alkaline phosphatase level is noted. The liver function is assessed by a complete blood count and comprehensive metabolic panel, including liver function tests and alkaline phosphatase levels. Brain MRI is only needed if symptoms are suggestive [25, 27].

All patients with a clinically or radiologically suspicious breast lesion require a biopsy to confirm the findings. A core needle biopsy is preferably obtained by US or stereotactic

guidance and must be done before any type of treatment is initiated. As a minimum, US-guided fine-needle aspiration or core biopsy of suspicious lymph nodes should be carried out, preferably followed by clip or carbon marking of biopsied lymph nodes [25, 27, 28].

Final pathological diagnosis should be made according to the tumor, node, metastasis (TNM) staging system (Table 2.). It provides an anatomical classification and is the most significant and predictive factor which will determine the survival rate is the stage of the tumor during the diagnosis. Specific description is the key for the selection of a correct method of treatment, the possible outcome, and the limitation for certain activities [25].

Table 2. TNM classification [29].

Stage	Description
NONINVASIVE	
0	No evidence of cancer cells or invasion of the basement membrane of the duct or neighboring normal tissue; includes ductal carcinoma in situ
INVASIVE	
IA	Tumor ≤ 2 cm AND No spread outside the breast; no lymph nodes involved
IB	No tumor in the breast, but microscopic metastases (>0.2 mm but ≤ 2 mm) present in axillary lymph nodes OR Tumor present in the breast, ≤ 2 cm, with involvement of lymph nodes
IIA	No tumor in the breast, but microscopic metastases (>2 mm) in 1-3 axillary lymph nodes OR Tumor ≤ 2 cm, with spread to axillary lymph nodes OR Tumor > 2 cm but <5 cm, with no spread to axillary lymph nodes
IIB	Tumor > 2 cm but ≤ 5 cm, with spread to 1-3 axillary lymph nodes OR Tumor > 5 cm, with no spread to axillary lymph nodes
IIIA	No tumor in the breast or presence of a breast tumor of any size associated with metastases in 4-9 axillary lymph nodes or in internal mammary nodes OR Tumor > 5 cm, with spread to axillary and/or internal mammary nodes
IIIB	Tumor of any size, with spread to the chest wall and/or skin of the breast; may also have spread to axillary or internal mammary nodes

IIC	Tumor of any size, with spread to ≥ 10 axillary lymph nodes OR Spread to lymph nodes above or below the collarbone (supraclavicular nodes) OR Spread to both axillary lymph nodes and internal mammary nodes
METASTATIC	
IV	Spread of cancer to other parts of the body such as liver, lung, or bone

4.5. Prevention

The aim of prevention is to lower the chance of getting cancer or assess cancer before it causes irreversible damage [30]. Different ways to prevent cancer are being studied, including avoiding well-established risk factors, performing early genetic tests or risk-reducing surgery, and implementing pharmacologic treatment of a precancerous condition [31]. However, the major role belongs to the screening programs that are widely implemented around the world and focus on early breast cancer detection, ie, prior to feeling a breast lump. Mammography is a preferred screening modality. Whether screening is needed depends on the women's age. WHO suggests screening for women aged 50-69 years, every 2 years, and recommends against screening for women 40-49 years of age and 70-75 years of age [32]. In Lithuania, a national breast screening program follows WHO's recommendations and screening mammography is available to all women from 50 to 69 years of age every 2 years. Further steps in breast cancer treatment depend on the results of the mammography [33].

5. Conclusions

1. The incidence and mortality rates of breast cancer increase every year and according to the WHO, it became the world's most prevalent cancer in 2020.
2. Well-established breast cancer risk factors are nonmodifiable such as gender, aging, genetic

predisposition, history of breast cancer in the family, race, reproductive system factors such as early menarche, late menopause, late age at first pregnancy, low parity, and lifestyle-related such as obesity, alcohol consumption, smoking.

3. Majority of cases are asymptomatic in early stages. Later, it develops to locoregional disease which includes breast and regional lymph nodes. Due to the spread of neoplasm metastatic disease may occur and it generally involves lungs, bones, liver and brain.

4. Diagnostics is based on symptoms and physical examination with following US-guided biopsy, which is the gold standard for confirming a diagnosis.

5. The main prevention method is screening mammography. WHO suggests to implement it for all women from 50 to 69 year of age every 2 years.

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