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Epidemiological models for breast cancer risk estimation

Epidemiologiczne modele szacujące ryzyko zachorowania na raka sutka

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Abstract

Breast cancer is the most common malignancy affecting women worldwide. Effective prevention and screening are only possible if there is precise risk prediction for cancer in an individual patient.
Mathematical models for estimation of breast cancer risk were developed on the basis of epidemiological studies. It is possible to identify women at high risk for this disease using patient history data and the analysis of various demographic and hereditary factors. The Gail risk model, originally developed in the United States to selectively identify patients for breast cancer chemoprevention studies, remains to be the most widely used and properly validated. The Cuzick-Tyrer model is more advanced and was developed for the International Breast Intervention Study (IBIS-1). It incorporates the assessment of additional hereditary factors, body mass index, menopausal status and hormone replacement therapy use. Genetic models aiming at calculating individual risk for BRCA1 and BRCA2 mutation carrier-state have also been designed.
In this review we discuss the usefulness of various risk estimation models and their possible application for breast cancer prophylaxis.

Key words: **breast cancer** / **risk assessment** / **statistical models** / **chemoprevention** /

Streszczenie

Rak piersi jest najczęstszym nowotworem złośliwym występującym u kobiet w Polsce i na świecie. Warunkiem odpowiedniego postępowania profilaktycznego i skriningowego jest możliwie precyzyjne określenie ryzyka wystąpienia nowotworu u danej pacjentki.
Na podstawie badań epidemiologicznych zostały opracowane matematyczne modele służące do szacowania ryzyka raka. Przy ich zastosowaniu na podstawie relatywnie prostych danych wynikających z wywiadu lekarskiego oraz analizy czynników demograficznych i rodzinnych można wyselekcjonować pacjentki, u których ryzyko rozwoju choroby nowotworowej jest podwyższone. Jednym z takich modeli, najpopularniejszym i najdokładniej przebadanym na świecie jest model Gail'a opracowany w Stanach Zjednoczonych jako narzędzie identyfikujące pacjentki do chemoprofilaktyki antyestrogenowej.

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Innym, bardziej zaawansowanym modelem jest model Cuzick-Tyrer opracowany na potrzeby badania International Breast Intervention Study (IBIS-1). Uwzględnia on dokładniejszą ocenę czynników dziedzicznych, a także wskaźnik masy ciała, stan menopauzalny oraz przyjmowanie hormonalnej terapii zastępczej. Opracowane zostały również modele czysto genetyczne służące do obliczania ryzyka nosicielstwa mutacji genów BRCA1 oraz BRCA2.
W niniejszej pracy rozważona jest użyteczność różnych modeli szacowania ryzyka oraz możliwości ich zastosowania w profilaktyce raka sutka.

Słowa kluczowe: **rak sutka** / **ocena ryzyka** / **modele statystyczne** / **chemioprofilaktyka** /

Introduction

Breast cancer is the most common malignancy affecting women. According to reports from the Maria Skłodowska-Curie Institute of Oncology, Warsaw, in 2007 breast cancer was diagnosed in more than 14 thousand women in Poland. It was followed by colon, lung and endometrial cancer. In the same year, more than 5 thousand patients died from breast cancer. The standardized breast cancer incidence and mortality rates for 2007 were 47,7 and 14,5 per 100000 women, respectively. In highly developed Western countries breast cancer incidence is significantly higher [1-3]. (Table I).

In the past decades, breast cancer incidence rate in Poland has been on steady increase, which is most likely related to the increasing prevalence of oncologically unfavorable demographic and reproductive profiles of the society. The mortality rate remains fairly stable which reflects improvements in diagnosis and treatment. Unfortunately, more advanced-stage cancers are diagnosed in Poland and 5-year survival rate is lower than in the United States and Western Europe. In comparison, Sweden has about twice the Polish incidence rate but identical mortality rate. (Table I).

Table I. Standardized breast cancer incidence and mortality rates (per 100000 women) in selected countries in 2007 [1-3].

Country	Incidence rate	Mortality rate
United States	123,8	24,5
Sweden	80,2	14,5
Poland	47,7	14,5

Currently, Poland has a well-designed mammography screening program starting at 50 years of age. However, prophylactic examinations and preventive care for younger women are not readily available in spite of recommendations of both national and international medical societies [4, 5].

Due to limited resources in the health care system, it is important for physicians to be able to identify women at risk for developing breast cancer who may benefit from early and intensive prophylaxis. A number of mathematical risk models based on epidemiological studies have been designed to meet such demand.

Gail Risk Model

Although it is possible to assess the risk factors for breast cancer individually when counseling a patient, this method cannot be standardized properly and thus translated into clinical decision-making. When the option for breast cancer chemoprevention with tamoxifen was introduced in the mid-80s, a new model for the risk prediction was needed [6]. Optimally, an absolute risk model can be constructed from a sufficiently large database of patients divided into subgroups with every possible combination of risk factors. Each subgroup should be large enough for absolute risk for developing cancer to be computed from a simple life expectancy table. Understandably, such a method would be impractical due to a sheer sample size required to obtain accurate results. Indirect methods that rely on estimates for relative risk associated with each factor are necessary.

In 1989 Mitchell Gail, a biostatistician working for the National Cancer Institute, MD, USA designed a mathematical model for breast cancer risk estimation [7]. The basis for this model were results from a large screening study known as the Breast Cancer Detection Demonstration Project which included 284780 women who had been undergoing annual mammographic examinations [8]. Dr Gail and his associates identified several key risk factors and estimated their relative risk values; which for individual factors were multiplied by each other, projected on the basic risk and converted into percentage values.

Exact mathematics aside, the Gail model provides an estimated risk for developing breast cancer in a particular patient for any subsequent time period. In most concomitant studies utilizing the Gail model, risk assessment was limited to 5 years and lifetime (up to 90 years of age). Since its publication, the original Gail model underwent some modifications limiting its application to invasive cancer risk only, incorporating atypical hyperplasia in breast biopsy as a new risk factor and adding effects of race or ethnicity [9].

Table II summarizes data necessary for breast cancer risk assessment with the modified Gail model. The National Cancer Institute has published an online calculator based on this model as a counseling tool for both patients and medical professionals (available at http://www.cancer.gov/bcrisktool/).

The Gail model was thoroughly validated in various settings and its strengths and limitations were recognized. It was primarily designed for the general population where epigenetic risk factors predominate over positive familial history. The history of cancer in the first degree relative is both the single most important risk factor and the only hereditary risk factor taken into account. Male breast cancers and ovarian cancers occurring in patient family, as well as age at diagnosis were also disregarded.

Table II. Data required to calculate breast cancer risk from the modified Gail model.

• **Medical history of any breast cancer or of ductal carcinoma in situ (DCIS), or lobular carcinoma in situ (LCIS)**
• **Age**
• **Age at the time of first menstrual period**
• **Age at the time of first live birth**
• **Number of first-degree relatives (mother, sisters, daughters) who had breast cancer**
• **Whether or not breast biopsy was performed**
• **Number of breast biopsies (positive or negative)**
• **Number of breast biopsies with atypical hyperplasia**
• **Race/ethnicity**

Since the vast majority of breast cancers occurs sporadically, the Gail model was highly successful in predicting the number of cancer cases in the general population. Rockhill et al. reported the expected to observed (E/O) cases ratio to be 1.03 (95% confidence interval (CI) – 0.88-1.21) in women screened regularly with mammography [10]. An Italian study by Decarli et al. gave comparable results – E/O of 0.93 (95% CI 0.81-1.08) [11].

Two major weaknesses of the Gail model were depreciation of the risk in patients with strong positive family history and relatively low predictive value for the development of cancer in an individual patient. Therefore, genetic specialists at the outpatient departments dealing with familial breast cancer ought to be careful when using the Gail model and should emphasize its limitations in their counseling. Patients should be reassured that high estimated risk does not imply the certainty of developing cancer in the future and, on the other hand, low estimated risk does not warrant less stringent adherence to screening programs. Additional issue with the Gail model is its reliance on regular mammographic examinations for accurate estimation. In younger women who are mostly unscreened, the Gail model may slightly overestimate the risk.

The first clinical application for the Gail model was to qualify patients for the Breast Cancer Prevention Trial (BCPT). This first randomized placebo-controlled trial for breast cancer chemoprevention with tamoxifen included women with 5-year risk for developing cancer of at least 1.66% (1 or more cases in 60 women) [12]. The study has successfully shown a 49% decrease in the incidence of invasive cancers in the tamoxifen pretreated group. However, the beneficial effects were limited to estrogen-positive cases. Further studies and meta-analyses confirmed the observed results [13].

According to recommendations by the U.S. Preventive Services Task Force currently in effect, preventive use of tamoxifen and raloxifen should be based on the elevated Gail risk score with the same cut-off value as in the BCPT trial. Although cancer chemoprevention falls outside of the scope of this review, it is should be emphasized that the BCPT selection criteria for the Gail score only lowered the number needed to treat, reducing exposure to potentially dangerous drug, and made sample sizes feasible to accrue. The results with regards to cancer prevention are likely to be similar in general population but the side effects of tamoxifen would prevail over its benefits.

Genetic Models

Genetic risk models neglect demographic and reproductive risk factors and focus only on the family history for breast cancer. The most popular is the Claus model [14]. Based on a large case-control study of 9418 women, it used sophisticated genetic analyses to identify a hypothetical autosomal allele responsible for increased breast cancer risk. The allele effect is age-dependent and unveils more often in younger women. In general population, one in 300 women is a carrier. Frequency increases with positive family history and respective odds may be calculated from the number of affected relatives. The elevated probability for the allele carrier increases the overall cancer risk above that observed in general population (10% in the United States at the time of the original study by Claus et al.). Unfortunately, lack of epigenetic risk factors confers to even lower predictive values than the Gail model. Amir et al. have shown that predictive accuracy expressed by the area under receiver-operator characteristic (ROC) curve was 0.735 for the Gail model and 0.716 for the Claus model [15]. Concordance of the Gail and Claus models in individual cases has been shown to be low [16].

Other genetic risk models (BRCAPRO and BOADICEA) took the risk assessment from a different perspective [17, 18]. With the analysis of lineage, they estimated the risk of the given individual for BRCA1 and BRCA2 mutations. If the risk exceeds 20% (10% in the United States), then genetic testing may be warranted [19]. The primary application for these models is cost-effective qualification for genetic profiling but they could be used for risk assessment. The overall breast cancer risk can be calculated as a product of carrier-state probability and the risk for developing cancer with BRCA1 and BRCA2 mutations.

Genetic models should best be used in specialist breast cancer prevention clinics where the positive family history is the main reason for referral.

Cuzick-Tyrer Risk Model

The only model incorporating multiple epigenetic risk factors and extensive family history is the Cuzick-Tyrer risk model [20]. It was developed as an alternative to the Gail model for qualification of patients for the International Breast Intervention Study (IBIS-1) [21]. The study was primarily based in the United Kingdom, Australia and New Zealand. Although positive family history and hyperplasia or lobular carcinoma in situ in previous breast biopsies were the primary inclusion criteria, patients with an estimated 10-year risk for developing breast cancer of 5% or more were also considered for inclusion.

The model used in the IBIS trial was subsequently published and is now available for downloading at http://www.ems-trials.org/riskevaluator/. It provides an in-depth pedigree analysis of the first and second degree relatives, including both breast and ovarian cancer cases, age at diagnosis and occurrence of bilateral disease. Possible results of genetic testing, menopausal status, use of hormone replacement therapy and body mass index are

taken into consideration as well. The model calculates predicted absolute lifetime and 10-year risk for developing breast cancer as well as risk for being BRCA1 or BRCA2 carrier from the family tree analysis.

Amir et al. who compared different risk assessment models in women with positive family history found that the Cuzick-Tyrer model was the most accurate for the E/O ratio of 0.81 (95% CI 0.62-1.08) and the area under ROC curve of 0.762. Expectedly, the Gail model seriously underestimated the risk in the study population [15].

Discussion

Adjusting therapeutic and preventive interventions to the individual risk for developing various diseases has become a widespread approach, particularly in cardiovascular medicine. Breast cancer risk estimation models brought this concept into gynecologic oncology. Ideally, a woman presenting to a primary care physician or gynecologist with breast cancer prophylaxis should undergo triage with the most comprehensive risk model that would determine time for initiation, method and frequency of screening. Chemoprevention for high risk women should be considered.

A common clinical problem is whether or not to obtain a wide range screening mammograms in women in their forties. While it is commonly accepted and reflected in various national programs that screening should commence at 50 years of age, certainly there are also younger women who would benefit from such examinations. If we assume that a 50-year old woman with no risk factors should be screened, then any younger women whose estimated risk equals or exceeds that for the former should be screened, too [22]. Appropriate calculations could be easily made with the Gail or Cuzick-Tyrer risk models.

McPherson et al. found that by using the presented rationale about 75% of unscreened patients who were diagnosed with breast cancer in their forties should have been recommended for earlier mammography [23]. The study did not consider, however, the increased breast density in younger women and difficulties in obtaining diagnostic images in that age group. Increased radiological breast density by itself is one of the strongest risk factors for breast cancer. Boyd et al. have demonstrated a 5-fold increase of breast cancer incidence (95% CI 3.6–7.1) in women who had more than 75% of glandular tissue on their screening mammograms [24]. Regrettably, this factor was not implemented in any of the risk models.

Breast cancer risk models have the potential to become useful tools in the Polish population. Adjustments should be made to reduce cancer incidence and overall lifetime risk. Further studies are needed as this subject coverage in the Polish literature is scarce.

The authors declare no conflict of interests.

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