SCREENING STRATEGY MODIFICATION BASED ON PERSONALIZED BREAST CANCER RISK STRATIFICATION AND ITS IMPLEMENTATION IN THE NATIONAL GUIDELINES - PILOT STUDY

SPREMEMJENI MODEL PRESEJANJA GLEDE NA IZRAČUN INDIVIDUALIZIRANE OGROŽENOSTI ZA RAKA DOJK IN MOŽNA IMPLEMENTACIJA PRESEJANJA GLEDE NA KATEGORIJO OGROŽENOSTI V DRŽAVNE SMERNICE - PILOTNA RAZISKAVA

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ABSTRACT

Keywords:
Tyrer-Cuzick model, breast cancer risk assessment, personalized breast cancer screening, breast cancer

Background: One of the most consistent models for estimating personalized breast cancer (BC) risk is the Tyrer-Cuzick algorithm that is incorporated into the International Breast Cancer Intervention Study (IBIS) software. Our main objective was to provide criteria for the classification of the Slovenian population, which has BC incidence below the European average, into risk groups, and to evaluate the integration of the criteria in Slovenian guidelines. Our main focus was on women age <50 with higher BC risk, since no organized BC screening is available for these women.

Methods: Slovenian age-specific BC risks were incorporated into IBIS software and threshold values of risk categories were determined. Risk categories were assigned according to the individual’s ten-year risk for women aged 40 and older, and lifetime risk for women between 20 and 39. To test the software, we compared screening strategies with the use vs. no use of IBIS.

Results: Of the 197 women included in the study IBIS assigned 75.1% to the BC risk group, and the rest to the moderately increased risk. Without IBIS 80 women were offered mammographic and 33 ultrasound screening. In contrast, 28 instead of 80 would have been offered mammographic screening and there would have been no referrals for ultrasound if IBIS had been used.

Conclusions: The Slovenian IBIS has been developed, tested and suggested for personalized breast cancer risk assessment. The implementation of the software with the consideration of Slovenian risk thresholds enables a more accurate and nationally unified assessment.

IZVLEČEK

Ključne besede: Tyrer-Cuzickov model, ocena ogroženosti za raka dojk, individualizirano presejanje za raka dojk, rak dojk

Uvod: Trenutno je kot najdoslednejši model za oceno individualizirane ogroženosti za raka dojk razpoznan Tyrer-Cuzickov algoritem, vključen v program IBIS (International Breast Cancer Intervention Study), ki temelji na angleških podatkih o incidenci raka dojk. Glavni cilj naših raziskav je bil postavitvi merila za razvrščanje slovenskih žensk, ki imajo ogroženost za raka dojk pod evropskim povprečjem, v skupine ogroženosti glede na izračun ogroženosti z uporabo programa IBIS. Prav tako smo želeli oceniti morebitno vplivajo teh meril v slovenske smernice. Poseben poudarek je namenjen bolj ogroženim pod petdesetim letom starosti, saj za ženske v teh starostnih skupinah nimamo organiziranega presejanja.

Metode: V programu IBIS smo umestili slovensko generacijsko specifično incidenco raka dojk in določili mejne vrednosti skupin ogroženosti (populacijska, zmerno povečana in visoka). Skupine ogroženosti so bile določene na podlagi 10-letne ogroženosti za ženske, ki so stare 40 let ali več, in doživljenjske ogroženosti za ženske, stare med 20 in 39 let. S programom IBIS smo izračunali ogroženost za raka dojk za ženske, ki so prišle na preventivni pregled v okviru primarnega in sekundarnega zdravstvenega varstva, in primerjali priporočila, ki so bila svetovana po pregledu, s priporočili, ki bi veljala, če bi uporabili program IBIS.

Rezultati: V raziskavo smo vključili 197 žensk in za vsako posameznico izračunali ogroženost za raka dojk s pomočjo programa IBIS. Program je 75,1 % žensk umestil v skupino populacijsko ogroženih, ostale pa v skupino zmerno povečane ogroženosti. Brez uporabe IBIS-a je bilo 80 žensk umesteno v bolj ogroženo skupino, opravili so presejalno mamborganijo, 33 ženkam pa so opravili ultrazvočno preiskavo dojk. Če bi uporabili nova merila razvrščanja v skupine ogroženosti s pomočjo izračuna programa IBIS, bi jih 28 namesto 80 opravilo presejalno mamborganijo. Prav tako bi nobene ženske po novih merilih poslali na ultrazvočno preiskavo dojk.

Zaključki: Razvili smo program IBIS, ki vsebuje slovensko populacijsko incidenco raka dojk. Program smo testirali in predlagali za orodje izračunavanja individualizirane ogroženosti za raka dojk. Uvedba programa bi, ob upoštevanju enotnih mejnih vrednosti kategorij ogroženosti, omogočala natančnejšo in bolj poenoteno obravnavo žensk na državni ravni.

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1 INTRODUCTION

Breast cancer is the most common cancer in women. Globally, more than 2 million women were diagnosed with breast cancer in 2018 (1). The average crude incidence rate in Slovenia has risen from 37.2/100,000 women in the period 1968–1972 to 127.2/100,000 in the period 2012–2016. Between the years 2012 and 2016 the average number of breast cancer in Slovenia was 1,279 annually (the average female population being 1,039,219 over this period) (2). The increase in the breast cancer burden is the result of the increasingly important role of reproductive risk factors (early menarche, later age at first full-term birth) and an aging population.

Evidence-based screening tests and early cancer detection followed by appropriate treatment decreases mortality and helps improve patients' quality of life. In Slovenia, a national breast cancer screening programme, DORA, offers biennial mammography to all women between the ages of 50 and 69 (3, 4). Recruitment is based solely on the participants' age, with a previous breast cancer diagnosis as an exclusion criterion. According to the current national regulation (Rules on Carrying Out Preventive Health Care at the Primary Level), women aged 20 to 50 are entitled to a clinical breast examination once every three years, performed by their gynaecologist at the primary level (5). If a woman is considered to be at higher risk, she is offered regular screening, as stated in the Table 1 (5).

Table 1. The summary of criteria for the higher risk women category and advised breast cancer screening tests according to current Rules on Carrying Out Preventive Health Care at the Primary Level (5).

| Criteria for higher breast cancer risk category (at least one of the following) | Screening tests at a Breast Unit for the higher breast cancer risk category (after the age of 40) |
| --- | --- |
| First full-term birth >30 years | Clinical breast examination (every 12-24 months) and Mammography and/or ultrasound examination of the breast or No screening is performed according to clinician decision |
| At least one relative (mother, sister, daughter) with breast cancer | |
| Personal history of breast disease that increases breast cancer risk | |
| Personal history of breast cancer in the past | |

However, these rules are in many ways outdated. Our data indicates that a substantial number of women are offered unnecessary mammography scans and are screened too often, especially those under the age of 50 (6). In 2018, the Slovenian breast cancer detection and treatment guidelines were therefore updated (7). These new guidelines recommend that women at higher risk should be screened according to their personal breast cancer risk. It is therefore very important to assess a woman’s risk even before she gets the invitation from the national breast cancer screening programme, since she might be at higher risk and should start with screening before the age of 50.

At the moment there are several different mathematical models available for personalized breast cancer risk assessment (8-11). Historically, the two oldest models are the Gail and Claus models (9-11). Both have numerous limitations, however, which have to be taken into account when performing the assessment and interpreting the results (12). The first studies using the Gail model indicated there was a tendency to overestimate the risk in younger women and to underestimate that in older women. As such, the model has recently been improved in order to correct some of these shortcomings (12-14).

Subsequently developed mathematical models, such as BOADICEA (the Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm), have proved to be more useful than their predecessors in the familial setting (15,16). At present, the Tyrer-Cuzick algorithm, which is incorporated into the IBIS (International Breast Cancer Intervention Study) software, is seen as the most consistent model for estimating breast cancer risk. IBIS includes both genetic and non-genetic risk factors in the assessment of breast cancer risk (17). Its algorithm is based not only on a woman’s family history and data on generation-specific population breast cancer risks, but also information on women's personal history, such as age, age at menarche and first full-term birth, parity, body height and weight, age at menopause and use of hormone replacement therapy as well as breast density and polygenic risk score (17). At the moment, IBIS software and BOADICEA are the most thoroughly validated models for calculating individual breast cancer risk (15, 17-19).

The software S-IBIS (Slovenian IBIS) for determining personalized breast cancer risk in the Slovenian population-based on Tyrer-Cuzick algorithm was developed and suggested for individual risk calculation (20). It is also presented as a possible tool for assessing breast cancer risk in the updated Slovenian guidelines (7).

The main objective of our study was to provide criteria for the division of our population into groups according to their individual breast cancer risk and to evaluate the impact of the new grouping algorithms on screening procedures. A special emphasis was given to women under 50, since no organized breast cancer screening is available for this age group.
2 METHODS

2.1 Data Source
In order to test S-IBIS and the newly-proposed risk categories we used data from women who visited either the regional Breast Unit (BU) in Kranj or a general practitioner working in the field of breast cancer prevention at the Primary Health Care Centre (PHCC) in Logatec (21, 22). Combining data from both pilot studies, 197 women were included in our analysis, 100 from BU and 97 from PHCC. Both centres represent locations in Slovenia at the primary health level where women may be assessed and referred for breast cancer screening.

All the personal and family history data necessary for the calculation of individual risk in the S-IBIS software (version-8) was collected during interviews. Additional information on the anticipated screening procedures (mammography, ultrasound examinations or just further appointments) was obtained from their health records. For each woman a personalized breast cancer risk was calculated with S-IBIS. According to the calculated 10-year or lifetime risk and age group, every woman was assigned to one of the Slovenian breast cancer risk categories: low risk, population risk, moderately increased risk, high risk. The McNemar test was used to determine if there were differences between the anticipated screening according to the current rules on carrying out preventive health care at the primary level and the screening according to the updated Slovenian guidelines (7).

SPSS version 24 (IBM Corp., Armonk, NY, USA) was used for the statistical analyses.

2.2 Personalized Breast Cancer Risk Evaluation Tool IBIS and Its Adjustment to Slovenian Population
The Tyrer-Cuzick model has been shown in several independent studies to be the most consistently accurate when compared with other models, in other words it performs accurately in the identification of a moderately increased to high risk of developing breast cancer, and currently it is the tool that includes the largest number of established breast cancer risk factors (23). The model has been incorporated into a computer programme, the IBIS software, which gives a personalized breast cancer risk estimate (17). The Tyrer-Cuzick model (now in version-8) combines family history, endogenous hormonal factors, benign breast disease, and other risk factors such as age, body mass index, hormone replacement therapy use, and mammographic density, as well as genetic factors (including BRCA and a polygenic risk score) into a single statistical model. The program assumes that there is genetic but yet unknown gene predisposing to breast cancer, in addition to the BRCA1/2 genes, to account for the remaining familial risk not explained by BRCA1/2. The woman's family history is used to calculate the likelihood of her carrying a pathogenic genetic variant, which in turn affects her likelihood of developing breast cancer. The phenotype of the woman can be modelled by (17):

\[ \text{Phenotype} = \begin{pmatrix} n_0 \\ BRCA1 \end{pmatrix} \left( \begin{pmatrix} n_0 \\ BRCA2 \end{pmatrix} \right) \]

where the first column contains information about the pathogenic variant in BRCA genes and may either contain the normal allele, a BRCA1 mutated allele or a BRCA2 mutated allele. The second column contains an adverse gene (the “low penetrance gene”) which was created to act as a surrogate for the effect of all the other “unknown” genes and which causes an increase in the relative hazard of breast cancer. This low penetrance gene is dominant so that a woman with two copies will have the same phenotype as a woman with one copy. To estimate this risk from family history (caused by the adverse genes), the model fits the results of the study done by Anderson et al. (24).

The family history of breast and ovarian cancer of the woman’s blood relatives is used to calculate the distribution of her genotype probabilities, which is used in calculation of the phenotypic probabilities. For a woman the absolute risk (Pr) of developing breast cancer between ages \( t_1 \) and \( t_2 \) is given by (17):

\[ \Pr(\text{cancer}) = 1 - \left( 1 - \sum_{i=1}^{6} p_i F_i(t_1, t_2) \right)^a \]

where \( p_i \) is the probability of the woman having the relevant phenotype, \( F_i(t_1, t_2) \) is the probability of getting breast cancer between ages \( t_1 \) and \( t_2 \) given the woman’s phenotype \( i \) and \( a \) is the relative risk due to personal factors. The IBIS software routinely estimates the likelihood of a woman developing breast cancer specifically within 10 years of her current age and over the course of her lifetime. The tool is not intended to assess the risk for women who have already been diagnosed with breast cancer (25).

For the purpose of this study, IBIS software was adjusted using Slovenian specific population breast cancer risks. Breast cancer incidence and mortality rates for the period 2006-2010 were obtained from the population-based Slovenian Cancer Registry (2).

2.3 Calculation of the Threshold Values
The calculations of threshold values of breast cancer risk categories for Slovenian women followed the procedures used in the development of the English guidelines (NICE - National Institute for Health and Care Excellence) (26-28). The direct application of the NICE threshold values of breast cancer risk categories would not be appropriate, however, because the Slovenian population risk of breast cancer is about 10% lower compared to the English.
population risk (29). The appropriate threshold values for Slovenian women were thus determined based on the data on the cumulative 10-year and lifetime breast cancer risks from the Slovenian Cancer Registry.

In the NICE guidelines, which are internationally available and therefore might be used by other countries, the decision to define moderately increased breast cancer risk with a threshold of 3% 10-year risk at age 40 years (or 17% lifetime risk) was taken as that is a level of risk equivalent to the average population risk of a 50-year old woman eligible for breast screening through English national breast screening programmes.

On the other hand, in Slovenia, a level of risk equivalent to the average population risk of 50 to 59 year-old women is lower, at about 2%, so the same 2% for 10-year risk was considered to be a threshold value for moderately increased risk at the age of 40. The upper threshold of moderately increased risk category for those aged 40 and 49 was set as five times the 10-year risk in the same age group. In the Slovenian female population aged 40-49 the 10-year risk was 1.3% in period 2011-2015, so the upper threshold value was set at 6.5% (the number is rounded up). For the age groups 50-59 and 60+ the lower threshold value of the moderately increased risk category was set as two times the 10-year relative risk (1.9% and 2.8%, respectively) yielding thresholds of 4.0% and 5.5% (the numbers are rounded for future use in practice); the upper threshold values remained the same as for the age group 40-49 (20).

For women in their twenties, it is more reasonable to report their lifetime risk. In our project, the calculation was done for a woman aged 25 years: first, using S-IBIS software we created a hypothetical case of a woman aged 40 with a family history of only one first- or second-degree relative diagnosed with breast cancer at older than age 40 who is at a 2% 10-year risk of developing breast cancer. By only changing the age from 40 to 25 the moderately increased risk threshold was obtained. The calculated lifetime risk of this woman was 16%, so the threshold for moderately increased risk in those aged between 20 and 39 was set at 16% or greater (20).

## RESULTS

### 3.1 Characteristics of the Studied Women According to Breast Cancer Risk Factors

In the study we calculated breast cancer risk scores of 197 women that consecutively attended preventive visits at the Breast Unit or Primary Health Centre and agreed to participate in the study, using S-IBIS software. In Table 2 we present the characteristics of the women studied according to breast cancer risk factors (age, family history, age at menarche, age at first full-term birth).

| Age groups          | Number of women | Percent (%) |
|---------------------|-----------------|-------------|
| 20-39 years         | 87              | 44.2        |
| 40-49 years         | 104             | 52.8        |
| 50-59 years         | 6               | 3.0         |
| Family history      |                 |             |
| positive            | 62              | 31.5        |
| negative            | 135             | 68.5        |
| Age at menarche     |                 |             |
| <11 years           | 7               | 3.6         |
| 11-12 years         | 57              | 28.9        |
| 13-14 years         | 108             | 54.8        |
| >15 years           | 25              | 12.7        |
| Age at first full-term birth |       |             |
| <25 years           | 81              | 41.1        |
| 25-29 years         | 54              | 27.4        |
| >30 years           | 31              | 15.7        |
| nulliparous         | 31              | 15.7        |

### 3.2 Breast Cancer Risk Categories for the Studied Women

For the division into breast cancer risk categories the newly calculated breast cancer risk thresholds for Slovenian women were used (Table 3). Table 3 presents the calculated breast cancer risk thresholds that are suggested for the division of women into risk categories according to the individual's ten-year risk for women age 40 and more, and lifetime risk for women between 20 and 39 (20).
Table 3.  Breast cancer risk categories for Slovenian women.

| Breast cancer risk category | Low risk (%) | Population risk (%) | Moderately increased risk (%) | High risk (%) |
|-----------------------------|--------------|----------------------|-------------------------------|---------------|
| Lifetime risk between ages 20 and 39 | - | <16 | 16 and higher | >30 |
| 10-year risk between ages 40 and 49 | - | <2.0 | 2.0 to 6.5 | >6.5 |
| 10-year risk between ages 50 and 59 | <1.3 | 1.3 to <4.0 | 4.0 to 6.5 | >6.5 |
| 10-year risk from age 60+ | <1.3 | 1.3 to <5.5 | 5.5 to 6.5 | >6.5 |

Based on the population of Slovenia and its average lifetime risk to develop breast cancer (i.e. up to age 85), women with a lower risk were assigned to the lower risk category, women with a risk that was 2- to 3-fold that of the population (16% - 29% lifetime risk) were assigned to the moderately increased risk category, and women with a lifetime risk of 30% and above the population risk were assigned to the high breast cancer risk category. Since the risk may vary over a woman’s lifetime, we also set the cut-off values for 10 year-risk groups (40-49, 50-60, and 60+ years) as defined in Table 3 (20).

By using S-IBIS and newly calculated breast cancer risk categories, a total of 197 women were assigned to breast cancer risk groups. Of these, 148/197 (75.1%) were assigned to the population risk category and 49/197 (24.9%) to moderately increased risk category, and none to the high or low risk categories.

3.3 Evaluation of the Impact of the New Grouping Algorithms on Screening Procedures

The comparison of anticipated mammographic and ultrasound screening (according to the current rules on carrying out preventive health care at the primary level) in women who visited preventive centres, and the foreseen screening according to the new Slovenian guidelines, are presented in Tables 4 and 5, respectively.

Table 4. Comparison of anticipated mammographic screening and screening foreseen in the new Slovenian guidelines by breast cancer risk categories and age groups.

| Breast cancer risk category | Anticipated mammographic screening (number of women) | Mammographic screening according to the new Slovenian guidelines (number of women) |
|----------------------------|-----------------------------------------------|----------------------------------------------------------------------------------|
|                            | Population risk | Moderately increased risk | Population risk | Moderately increased risk |
| Ages between 20 and 39     | 5                | 4                        | 0              | 0               |
| Ages between 40 and 49     | 43               | 27                       | 0              | 34              |
| Ages between 50 and 55     | 1                | -                        | 6              | -               |
| All ages                   | 49               | 31                       | 6              | 34              |

*Risk category was determined by S-IBIS calculation, and division into risk groups was performed as proposed in Table 3.

Table 5. Comparison of anticipated ultrasound screening for breast cancer prevention and screening foreseen in the new Slovenian guidelines by breast cancer risk categories and age groups.

| Breast cancer risk category | Anticipated ultrasound screening (number of women) | Ultrasound screening according to the new Slovenian guidelines |
|----------------------------|--------------------------------------------------|-------------------------------------------------------------|
|                            | Population risk | Moderately increased risk | Population risk | Moderately increased risk |
| Ages between 20 and 39     | 7                | 3                        | -               | -               |
| Ages between 40 and 49     | 14               | 9                        | -               | -               |
| Ages between 50 and 55     | 0                | -                        | -               | -               |
| All ages                   | 21               | 12                       | According to the new guidelines ultrasound screening is recommended only upon referral from a radiologist |

*Risk category was determined by S-IBIS calculation, and division into risk groups was performed as proposed in Table 3.
Out of the 148 women who fall into the population risk category, 49 (33.1%) were deemed suitable for mammographic screening according to the current rules of primary practice, while 31 (63.3%) women out of 49 were in the moderate risk category. Thus, from all of the 197 women included in the pilot studies, 80 (40.6%) would be eligible for mammographic surveillance until the age of 55. In contrast, with the implementation of the new Slovenian guidelines, only six women from the population risk category and 34 (17.3%) from the moderate risk category would be eligible for mammographic screening. All women above the age of 50 would be offered mammographic screening in the population-based organized screening program that is already available.

When comparing both approaches, 28 women of 80 who were offered mammographic screening according to the current rules, would also be offered mammographic screening according to the new guidelines. On the other hand, 12 women out of 117 that were not offered mammographic screening by current rules would be offered it with the implementation of the new guidelines. An exact McNemar’s test determined that there was a statistically significant difference between current practice and the new Slovenian guidelines for mammographic screening, at p<0.001.

In the population risk category, 21 (14.2%) women out of 148 had ultrasound screening, in the moderately increased risk category it was 12 (24.5%) women out of 49, giving a total of 33 (16.8%) out of 197 women. With the implementation of the new Slovenian guidelines, ultrasound would only be performed on referral from a radiologist.

4 DISCUSSION

Our study results will help to update and re-design clinical pathways for the early detection of breast cancer in asymptomatic Slovenian women and to identify those women with an increased risk of breast cancer. Furthermore, these results will inform recommendations for the Breast Cancer Detection and Treatment Guidelines. In Slovenia, breast cancer screening procedures are currently defined in the national Rules on Carrying Out Preventive Health Care at the Primary Level that are authorized by the Ministry of Health (5). However, these are outdated, vague and non-specific, with an unreasonably broad definition of higher breast cancer risk, which results in unequal treatment of women who would have the same numerically assessed breast cancer risk. As a consequence of this unspecific risk categorization and broad definition of higher breast cancer risk, many women receive screening referrals too frequently and often unnecessarily. This, in return, leads to unnecessary cost and other negative effects, such as a psychological burden for the women and capacity issues for the screening units. The Institute of Oncology Ljubljana therefore implemented the guidelines of breast cancer diagnosis and treatment in 2018, where it is stated, among other points, that the breast cancer risk can be calculated with the help of specific risk assessment tools (7). A reliable personalized breast cancer risk assessment is essential for the provision of risk-benefit analysis prior to the initiation of any screening, preventive or diagnostics procedures (30).

In addition, it is of utmost importance to determine the Slovenian threshold values for the stratification of asymptomatic women into breast cancer risk groups, based on the S-IBIS software results, with these being the low, population, moderately increased and high breast cancer risk group. Our comparisons show that using the English population specific risks overestimates the risks for Slovenian women by up to 10%, but the comparison needs validation based on actual cases in the assessed cohort (29). We defined the threshold values in collaboration with experts from Slovenia and an expert from Great Britain who was involved in the development of the English guidelines (NICE - National Institute for Health and Care Excellence) (26-28).

We evaluated the use of the software and newly proposed thresholds. We measured probable changes in the existing work processes and evaluated the impact of the use of the software tool on screening procedures compared to the current practice under the existing rules. The S-IBIS was used for risk assessment on a sample of asymptomatic women who were mostly younger than 50 years and therefore not included in the national breast cancer screening programme, but were evaluated to be at moderately increased or high risk and so entitled to breast cancer screening under the existing rules.

The results clearly show it is reasonable to incorporate the use of S-IBIS into everyday practice. With regard to the current system, our study revealed that 40.6% (80 out of 197) women were referred to screening mammography. If the new guidelines were applied, by using risk category stratification, as explained in Table 3, only 14.2% (28) of women would be referred for further screening due to moderately increased or high breast cancer risk. It seems that we are currently offering mammography to women aged between 40-50 who are at population risk, mainly due to vague regulations. More than half of these women could wait until the age of 50 for the national screening program invitation. Based on our results, we expect that the number of screening mammograms that the public healthcare system is paying for would decrease if mammography were performed based on our proposed personal risk calculations. Such an approach would also offer equal opportunities to all Slovenian women.
The major limitation of our study was the sample size, since it represents only a small fraction of the Slovenian female population. On the other hand, it was the first attempt to numerically and systematically assess breast cancer risk in the Slovenian female population at the primary health care level, and to set the cut-off values for breast cancer risk categories in this group. These results provide us with the design of a clinical pathway for early detection of breast cancer among Slovenian asymptomatic women aged under 50 who are at an increased risk of breast cancer. Direct validation of these estimates based on 5- and 10-year risk will provide further validation of our findings.

In conclusion, the implementation of the developed and upgraded software S-IBIS for the calculation of the personalized breast cancer risk and implementation of new clinical pathways in the Slovenian health care system will bring more evidence-based referrals of asymptomatic women who are at increased risk of breast cancer. The number of unnecessary preventive procedures will decrease, and the waiting times for those who are eligible for higher risk screening will be reduced. This data is likely to be useful in other countries with lower than average European breast cancer incidence rates.

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CONFLICTS OF INTERESTS

The authors declare no conflicts of interest.

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ETHICAL APPROVAL

The National Medical Ethics Committee at the Ministry of Health from the Republic of Slovenia (No. 0120-404 / 2016-2 KME 60 /07 /16) approved the study.

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