research article

Breast cancer risk based on adapted IBIS prediction model in Slovenian women aged 40-49 years - could it be better?

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Radiol Oncol 2020; 54(3): 335-340.

Received 25 March 2020
Accepted 7 May 2020

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Disclosure: No potential conflict of interest were disclosed.

Background. The aim of the study was to assess the proportion of women that would be classified as at above-average risk of breast cancer based on the 10 year-risk prediction of the Slovenian breast cancer incidence rate (S-IBIS) program in two presumably above-average breast cancer risk populations in age group 40-49 years: (i) women referred for any reason to diagnostic breast centres and (ii) women who were diagnosed with breast cancer aged 40–49 years. Breast cancer is the commonest female cancer in Slovenia, with an incidence rate below European average. The Tyrer-Cuzick breast cancer risk assessment algorithm was recently adapted to S-IBIS. In Slovenia a tailored mammographic screening for women at above average risk in age group 40–49 years is considered in the future. S-IBIS is a possible tool to select population at above-average risk of breast cancer for tailored screening.

Patients and methods. In 357 healthy women aged 40–49 years referred for any reason to diagnostic breast centres and in 367 female breast cancer patients aged 40–49 years at time of diagnosis 10-years breast cancer risk was calculated using the S-IBIS software. The proportion of women classified as above-average risk of breast cancer was calculated for each subgroup of the study population.

Results. 48.7% of women in the Breast centre group and 39.2% of patients in the breast cancer group had above-average 10-year breast cancer risk. Positive family history of breast cancer was more prevalent in the Breast centre group ($p < 0.05$).

Conclusions. Inclusion of additional risk factors into the S-IBIS is warranted in the populations with breast cancer incidence below European average to reliably stratify women into breast cancer risk groups.

Key words: breast cancer; early detection; risk prediction model; tailored screening

Introduction

Breast cancer is the most common cancer in women with more than 2 million new cases diagnosed worldwide in the year 2018 and therefore represents a major public health problem. In Europe alone, the number of women diagnosed with breast cancer in 2018 was approximately 523 000 with an estimated age-standardized incidence rate of 100.9/100 000.[1] Breast cancer is the most common cancer in women in Slovenia as well and in 2016 there were 1386 new cases diagnosed. However, the age-standardized incidence rate in Slovenia is lower than European average rate (68.5/100 000 women).[2,3]

Mammographic screening is one of the established strategies to deal with the breast cancer problem in public healthcare. The Slovenian national mammographic screening program offers biennial screening mammography to all women in the age group 50–69 years.[4]

However, approximately one sixth of breast cancer patients are diagnosed at age 40 to 49 years, on average with a more advanced stage at the time of diagnosis compared to patients diagnosed in the age group 50–69 years.[2] Despite this fact, in Slovenia there is no organized mammographic screening program in this age group of women due to lack of convincing evidence that population mammographic screening reduces breast cancer mortality in women aged 40–49 years. Namely, according to European guidelines there is conditional recommendation against breast cancer screening for women aged 40 to 45 years, and only conditional recommendation for the screening for the age group 45 to 49 years.[5]

In Slovenia all breast cancer in the age group 40–49 years are diagnosed in regional diagnostic breast clinics whether due to symptomatic disease or as a result of opportunistic screening. Women can be referred to opportunistic screening by their gynaecologists or general practitioners based on family history of breast cancer or other risk factors. Women with high breast cancer risk (i.e. genetic predisposition) may opt for surveillance separately in a dedicated centre.

To overcome the limitations of the population screening in younger women, tailored breast cancer screening limited to women with an above-average breast cancer risk is one of the research options today. Based on the 2018 Slovenian recommendations on breast cancer prevention and treatment a tool is needed to stratify women according to 10-years breast cancer risk in three groups: population risk, moderately increased risk and high-risk group, respectively.[6] Only women at above the population risk should be offered screening before the age of 50.

To improve identification of women at above-average risk of breast cancer, many breast cancer prediction models have been developed in the last three decades.[7] The IBIS software, based on the Tyrer-Cuzick algorithm, is one of the most consistent, both in the general population and in familial setting.[8-10] IBIS calculates breast cancer risk based on classical risk factors including age, family history of breast or ovarian cancer in first- and second-degree relatives, age at menarche and menopause, parity and age at first childbirth.[8] Recently mammographic density and polygenic risk score were added as additional risk factors to be taken into account in the calculation of breast cancer risk.[11,12] However, these two risk factors are very seldom available in routine clinical setting. The IBIS program was developed with breast cancer incidence rates of the United Kingdom and was recently separately adapted for the Swedish and Slovenian populations (S-IBIS software).[13]

The IBIS program was validated on several populations, varying both in age and geographic location.[7,9,10,14,15] However, the performance of the recently adapted S-IBIS in Slovenian population is still unknown. We were particularly interested in S-IBIS performance in two presumably above the average breast cancer risk populations: (i) women aged 40 to 49 years referred for any reason to diagnostic breast centres and (ii) women who were diagnosed with breast cancer between the ages of 40 to 49.

The aim of our study was to conduct S-IBIS calculations in the two aforementioned groups of patients and determine the proportions of three 10-years breast cancer risk groups (population risk, moderately increased and high risk) in both group of patients.

Patients and methods

In this study two groups of patients were included:

1. 357 women aged 40–49 years attending opportunistic screening in 5 diagnostic breast centres in central Slovenia in year 2014;
2. 367 women aged 40–49 at time of breast cancer diagnosis, treated at the Institute of Oncology Ljubljana between 2014 and 2019. Patients are regularly followed up in outpatient clinics of the Institute of Oncology Ljubljana.

All women were asked to answer a questionnaire about established risk factors for breast cancer according to the IBIS requirements and family history of breast and ovarian cancer concerning first- and second-degree relatives (Table 1). Women in the breast cancer group were specifically asked to provide data available at their age of 40. Personal history of breast cancer diagnosis was not included in the risk calculation for the breast cancer group. Mammographic density and polygenic risk score could not be included in the risk calculation due to unavailable data, therefore these fields were left blank. Results of genetic testing were also not included as the testing was usually performed after the diagnosis of breast cancer in the breast cancer group. Women from the Breast centre group did not fill the criteria for genetic testing and the testing was therefore not performed.

Women with known genetic predisposition (i.e. BRCA and other mutations) were not included in the study. The majority of women who are carriers

TABLE 1. Breast cancer risk factors used for 10-year breast cancer risk calculation with S-IBIS software

Risk factor
Age (years)
Height
Weight
Age at menarche (years)
Age at first childbirth
Menopausal status
Hormone replacement therapy use
Benign breast disorder
Family history of breast cancer (breast cancer in first- and second-degree relatives and age at presentation)
Family history of ovarian cancer (ovarian cancer in first-degree relatives and age at presentation)

of a hereditary breast cancer related mutations are already followed up in a dedicated centre and they would not benefit from an improved population screening but may ultimately alter the proportion of women in the low and high-risk groups.

The participants were informed about the meaning and use of the provided data and signed an informed consent.

Based on the acquired data 10-year risk of breast cancer for each woman with the S-IBIS software was calculated.

For the purpose of a separate sub analysis the patients were divided in two subgroups, age 40–44 and age 45–49. In the breast cancer group there were 125 participants in the 40–44 years age group and 242 participants in the 45–49 years group, while in the breast centre group there were 153 participants in the 40–44 years age group and 204 participants in the 45–49 years group.

In breast cancer patient group the personal diagnosis of breast cancer was not included in the calculation of risk.

Breast cancer risk thresholds for the Slovenian population as described in the literature (population risk: below 2%, moderately increased risk: 2–6.5%, high risk: above 6.5%) were taken into account for assessment of performance of the S-IBIS software.[13]

IBM SPSS Statistics v25 was used to generate data analysis. Mann-Whitney and Chi-square tests was used to assess statistically significant differences in baseline data; $p < 0.05$ was considered statistically significant.

The study was approved by the National Ethics Committee.

TABLE 2. Baseline characteristics of participants

	Breast cancer group	Breast Centre group
Age (yaars, mean)*	45.6	44.8
BMI, mean (kg/m2)*	24.3	24.8
Age at menarche (years, mean)	13.0	13.0
Nulliparity	10.5%	11.1%
Age at first childbirth (years, mean)	23.0	23.4
Positive family history for breast and/or ovarian cancer*	48.8%	56.6%

* statistically significant difference was observed between the two groups ($p < 0.05$); BMI = Body mass index

TABLE 3. Risk stratification for all participants and for age subgroups 40–44 years and 45–49 years based on S-IBIS calculation for breast cancer patients and women screened in Breast centre; risk categories for women aged 40 to 49 as in 2018 Slovenian guidelines

	Population risk (< 2 %)	Moderately increased risk (2–6.5 %)	High risk (> 6.5 %)
Breast cancer group - 10-year breast cancer risk (age 40–49)	60.8 %	37.8 %	1.4 %
Breast centre group - 10-year breast cancer risk (age 40–49)	51.3 %	47.6 %	1.1 %
Breast cancer group - 10-year breast cancer risk (age 40–44)	64.0 %	34.4 %	1.6%
Breast centre group - 10-year breast cancer risk (age 40–44)	58.2%	41.8 %	0.0%
Breast cancer group - 10-year breast cancer risk (age 45–49)	59.1 %	39.7 %	1.2 %
Breast centre group - 10-year breast cancer risk (age 45–49)	46.1 %	51.9%	2.0%

Results

The baseline characteristics of the two groups regarding the breast cancer risk factors are reported in Table 2. Statistically significant differences where noticed between the two groups while analysing age, body mass index (BMI) and positive family history for breast and/or ovarian cancer, with participants in the Breast centre group being younger, with higher BMI and positive family history in more cases.

The risk calculations for the whole population and within each age subgroup are shown in Table 3.

Discussion

S-IBIS risk calculation based on the included participants' data identifies only 48.7% of women referred to Breast centres as above population breast

cancer risk (10 years risk > 2%). Furthermore S-IBIS as used in our study identifies as above the population risk 39.2% of women, who were diagnosed with breast cancer. It should be once again noted that some data such as mammographic density and polygenic risk score (PRS) that could be included in the risk calculation, could not be retrieved for the participants of our study. Still, the identification of almost 40% breast cancer patients as at above-average risk is a promising result, that is comparable to results of other studies.[10, 16-19] However it is still worrisome that as much as 60% of patients diagnosed with breast cancer in age group 40–49 would be diagnosed outside the screening program if women were invited to breast cancer screening based on S-IBIS risk calculation as it could be widely available at the present moment (that is, without data about mammographic density and PRS). Therefore our study showed that tailored mammographic screening in the age group 40–49 in Slovenian population cannot be organized based on this form of S-IBIS alone. Assuming the expected less than 100% attendance rate of the invited population and lower mammography sensitivity in this age group, the proportion of diagnosed cancers would be even lower. These data are in clear contrast to current Slovenian screening program in age group 50–69 in which 70% of all cancers in this age group are diagnosed within the screening program with an average 75% attendance rate.[2]

Interestingly, a higher proportion of women were identified as above population risk in healthy women referred to breast centres for opportunistic screening compared to breast cancer patients, 48.7% *vs*. 39.7%, respectively. One of the reasons could be the higher proportion of women with positive family history and higher BMI in the breast centre group. The reason for relatively poor performance of the S-IBIS could be caused also by some personal characteristics of Slovene women that differ from other European populations where IBIS was validated, e.g. the age at first childbirth in Slovenia is lower than European average.[20]

When analysing the S-IBIS performance separately in the 40–44 year and 45–49 year age subgroups, we found that S-IBIS performed slightly better in the age group 45–49 years compared to younger age group (40–44 years). The difference was not big enough however to allow to draw different conclusions between the subgroups studied.

Extension of mammographic screening to women younger than 50 is a matter of debate, although several studies have confirmed that the harms of early screening do not outweighs the benefits. Over-diagnosis and false positive recalls in women younger than 50 years and non-significant lower breast cancer mortality between younger and older breast cancer patients make early breast cancer screening unreliable and unadvisable in the general population.[21,22] However, the problem of early detection of breast cancer in women younger than 50 persists and as previously stated, screening of women at higher-than-average risk of breast cancer seems one of the most feasible solutions. Based on data presented, further steps in refining a breast cancer risk calculation tool will have to be done before a tailored screening is implemented, as the inclusion of more breast cancer risk factors like mammographic density. Mammographic density is considered as a strong risk factor for breast cancer and, as already mentioned, can be included in the S-IBIS calculation.[23-25] Another promising risk factor is the polygenic risk score (PRS) based on the presence of single nucleotide polymorphisms (SNPs) related to breast cancer risk and which can be also included in the S-IBIS calculation.[26-28] At the present moment, there are numerous different sets of SNPs being studied worldwide, none of them yet approved to routine use. Of note, several studies in European populations with higher than Slovenian breast cancer incidence have shown that both factors independently increase the sensitivity of IBIS.[27-30] Due to technical limitations both mammographic density and PRS are not routinely included in S-IBIS calculations throughout Slovenia, therefore currently no data on value of mammographic density and PRS in Slovenian population is available. Data are available for selected breast centres and are yet to be analysed at the time writing this article. Studies with S-IBIS risk calculations that include these risk factors are necessary and will have to be performed to further improve the stratification of women in the breast cancer risk groups and reveal the true potential of the S-IBIS program.

Our study had several limitations. Since it is a cross-sectional study, it lacks follow up and we could not observe the eventual crossover between the two groups. Only follow-up of the Breast centre group until the age of 50 would reveal the percent of overlap between the two groups and the true quality of risk stratification based on risks calculated by S-IBIS. Due to inability to assess the proportion of women undergoing early screening that would develop breast cancer before the age of 50, statistical comparison between the two groups was not performed, as it would lead to false assumptions. Furthermore, the non-systematic ac-

crual of women referred to opportunistic screening in Breast centres can result in high proportion of women at average breast cancer risk in the Breast centre group. Despite these limitations however, our study demonstrated the inability of the S-IBIS alone to reliably stratify women between the breast cancer risk groups. We acknowledge that a prospective study would give clearer and more reliable data, but in the given settings only a retrospective analysis was possible and perhaps necessary to plan a valid perspective study.

Conclusions

In conclusion, risk stratification based on S-IBIS calculation confirmed that at least half of women referred to regional Breast centres have above-average 10-year breast cancer risk and are entitled to regular screening prior to age 50 according to Slovenian guidelines. However, more than half of breast cancer patients aged 40–49 would not be selected for early tailored screening based on S-IBIS calculations with the chosen risk factors. Inclusion of additional risk factors (as mammographic breast density or PRS) into the S-IBIS is warranted in the populations with breast cancer incidence below European average to reliably stratify women into breast cancer risk groups. Tailored mammography screening in age group 40–49 based on S-IBIS alone can not be organized.

Acknowledgment

The study was supported by the research program of the Slovenian research agency P3-0352.

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