



The accuracy of breast cancer risk self-assessment does not correlate with knowledge about breast cancer and knowledge and attitudes towards primary chemoprevention

Kristina Bojanic^{a,b,c,1}, Sonja Vukadin^{d,e,1}, Kaja Grgic^e, Luka Malenica^f, Filip Sarcevic^e, Robert Smolic^{f,g,h}, Kristina Kralikⁱ, Aleksandar Včev^{f,g,h}, George Y. Wu^j, Martina Smolic^{d,e,*}

^a Department of Biophysics and Radiology, Faculty of Dental Medicine and Health Osijek, J. J. Strossmayer University of Osijek, Osijek 31000, Croatia

^b Department of Biophysics and Radiology, Faculty of Medicine Osijek, J. J. Strossmayer University of Osijek, Osijek 31000, Croatia

^c Department of Radiology, Health Center Osijek, Osijek 31000, Croatia

^d Department of Pharmacology and Biochemistry, Faculty of Dental Medicine and Health Osijek, J. J. Strossmayer University of Osijek, Osijek 31000, Croatia

^e Department of Pharmacology, Faculty of Medicine Osijek, J. J. Strossmayer University of Osijek, Osijek 31000, Croatia

^f Department of Patophysiology, Physiology and Immunology, Faculty of Dental Medicine and Health Osijek, J. J. Strossmayer University of Osijek, Osijek 31000, Croatia

^g Department of Patophysiology, Faculty of Medicine Osijek, J. J. Strossmayer University of Osijek, Osijek 31000, Croatia

^h Department of Internal Medicine, University Hospital Osijek, Osijek 31000, Croatia

ⁱ Department of Medical Statistics and Medical Informatics, Faculty of Medicine Osijek, J. J. Strossmayer University of Osijek, Osijek 31000, Croatia

^j Department of Internal Medicine, Division of Gastroenterology/Hepatology, University of Connecticut Health Center, 263 Farmington Avenue, Farmington, CT 06032, USA

ARTICLE INFO

Keywords:

Breast cancer
Breast cancer risk perception
BCRAT risk model
Chemoprevention
Knowledge
Attitudes

ABSTRACT

The increase of breast cancer (BC) incidence has drawn attention to BC risk as means of reducing mortality and morbidity of the disease. The aim of this study was to determine the accuracy of BC risk perception, evaluate factors that affect risk perception and assess the correlation between BC risk perception and attitudes towards BC chemoprevention. A cross-sectional study included total of 258 women with average and high-risk for BC according to the Breast Cancer Risk Assessment Tool (BCRAT). All data were collected by face-to-face interview by three trained 6th year medical school students using a 54-item questionnaire. Each participant's actual BC risk was compared to a perceived risk and the accuracy of the BC risk self-assessment was determined. 72% of high-risk women underestimated their BC risk ($p < 0.001$). One third of subjects with a family history of BC have also underestimated their own risk ($p = 0.002$). Women who responded to screening mammography were more informed about BC risk factors ($p = 0.001$). General knowledge about BC chemoprevention was surprisingly low, regardless of the accuracy of BC risk self-assessment. High-risk women appear to be unrealistically optimistic, since there was a significant difference between the accuracy of self-perceived risk and the objective BC risk.

1. Introduction

Breast cancer (BC) is the most common cancer in females accounting for 26% of all cancers in women. According to the Global Cancer Observatory by International Agency for Research on Cancer the BC incidence and mortality rate will continue to rise over the next 20 years to affect over 3 million people, and cause 992,000 deaths in 2040 (Bray

et al., 2018). In many Western countries, BC mortality has been declining in recent years, primarily as a result of better secondary prevention, detection of early-stage BC and improved treatment. The role of primary prevention of BC in general population, involving procedures that reduce the risk of disease, such as preventive mastectomy and chemoprevention, is insufficient. BC prevention strategies are far behind the prevention of cardiovascular diseases with routinely prescribed

* Corresponding author at: Dept. of Pharmacology, Faculty of Medicine Osijek and Dept. of Pharmacology and Biochemistry, Faculty of Dental Medicine and Health Osijek, University of Osijek, J. Huttlera 4, 31000 Osijek, Croatia.

E-mail addresses: kristina.bojanic@fdmz.hr (K. Bojanic), sonja.vukadin@fdmz.hr (S. Vukadin), kaja.grgich@gmail.com (K. Grgic), luka.malenica@fdmz.hr (L. Malenica), filip.sarcevic@gmail.com (F. Sarcevic), robert.smolic@mefos.hr (R. Smolic), kristina.kralik@mefos.hr (K. Kralik), avcev@fdmz.hr (A. Včev), wu@uconn.edu (G.Y. Wu), martina.smolic@mefos.hr (M. Smolic).

¹ Both authors contributed equally to this work.

<https://doi.org/10.1016/j.pmedr.2020.101229>

Received 16 May 2020; Received in revised form 11 October 2020; Accepted 13 October 2020

Available online 20 October 2020

2211-3355/© 2020 The Authors.

Published by Elsevier Inc.

This is an open access article under the CC BY-NC-ND license

(<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

antihypertensive, statins and antiplatelets (Meyskens et al., 2011). Although randomized controlled trials have shown that the use of chemoprevention with selective estrogen receptor modulators (SERMs) and aromatase inhibitors (AIs) (Cuzick et al., 2014, 2015, 2020; Dowsett et al., 2010; Cuzick, 2018; Goss et al., 2011) reduced BC risk by up to 50–65% among high-risk women, chemoprevention is still not widely utilized.

Women with a 5-year BC risk of at least 1.67% or a lifetime risk of 20% or greater, based upon the Gail model (Gail et al., 1989; Costantino et al., 1999) are defined as high-risk women for developing BC and may benefit from chemoprevention (Reimers et al., 2015; Owens et al., 2019). However, uptake and adherence to the BC chemoprevention is estimated to be extremely low and according to some studies prevalence of the earliest chemopreventive agent, tamoxifen, in high-risk women is less than 5% (Ropka et al., 2010; Hackett et al., 2018). Numerous barriers to the use of chemopreventive drugs have been identified to date, such as lack of physician knowledge about SERMs and AIs use, physician and patient concerns about medication side effects and poor assessment of patients’ own cancer risk (Ropka et al., 2010; Kartal et al., 2014; Park et al., 2009). A limited number of studies have examined the socio-demographic and clinical characteristics associated with uptake of chemopreventive therapy among high-risk women (Reimers et al., 2015; Hackett et al., 2018). Studies reported poor awareness and knowledge about BC in general population (Islami et al., 2017; Peltzer and Pengpid, 2014; Ryan et al., 2015). Data about BC risk perception are diverse and

contradictory among studies (Iwuji et al., 2014). Women who underestimate their personal BC risk are less likely to participate in screening programs and other primary prevention strategies (Park et al., 2009; Katapodi et al., 2010). On the contrary, the overestimation of BC risk results in unnecessary diagnostic procedures, needless interventions and anxiety (Xie et al., 2019; Speiser et al., 2019; de Jonge et al., 2009; Davids et al., 2004; Alexander et al., 1996). Accurate calculation and perception of personal BC risk are a critical part of primary and secondary BC prevention (de Jonge et al., 2009; Abittan et al., 2019; Metcalfe and Narod, 2002).

The aim of this study was to determine the accuracy of BC risk perception and knowledge about BC risk factors and BC chemoprevention, to evaluate factors that affect risk perception and to determine the correlation of BC risk perception and attitudes towards BC chemoprevention.

2. Materials and methods

2.1. Subject population

This was a single center cross-sectional study on 258 participants included after regular ultrasound or mammography examination and after screening mammography at the Osijek Health Center from February 2019 to January 2020. Participants, regardless of age, who were referred for a diagnostic breast ultrasound or mammographic examination, as

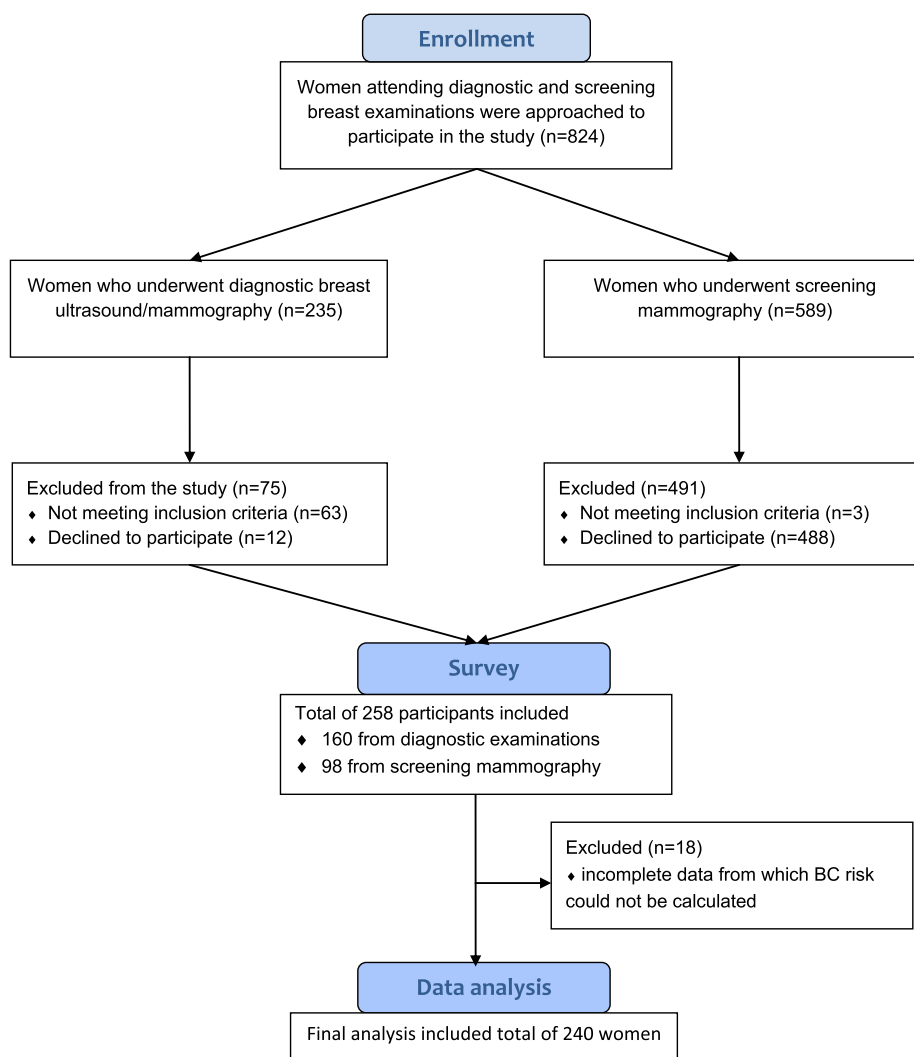


Fig. 1. CONSORT diagram. A concise graphic representation of the study flow.

well as women who were invited to have screening mammography were included successively, if they agreed to participate in the study and did not meet the exclusion criteria. The exclusion criteria included lack of data for calculation of the BC risk according to the BCRAT model, such as personal history of invasive BC, lobular carcinoma in situ (LCIS) or ductal carcinoma in situ (DCIS); positive result of genetic testing of the BRCA1 / BRCA2 gene; diagnosis of hereditary cancer-related syndrome based on genetic testing; previous radiotherapy treatment to the thorax. A concise graphic representation of the study flow is presented in the Fig. 1.

Ethical approval for this study was obtained from the Health Center Osijek Review Board (Approval number: 03-319-1/19). All research involving human subjects in this study was done in accordance with ethical principles outlined in the World Medical Association Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects (initiated in June 1964, last amendment in October 2000). All participants signed an informed consent form before being included in the study.

2.2. Study design and procedure

All data were collected by face-to-face interview by three trained 6th year Medical School students. A 54-item questionnaire, divided into 5 sections, was developed for the purpose of the study. The first part of the questionnaire examined the self-perceived BC risk and concerns about possible BC diagnosis; the second part examined the participants' knowledge about the BC risk factors; the third examined the anamnestic data needed to objectively assess the BC risk according to the BCRAT model and the participants' sociodemographic data; the fourth examined the knowledge about BC chemoprevention; and the fifth examined the participants' attitudes towards BC chemoprevention. The final structure of this questionnaire was determined by factorial analysis performed on 150 questionnaires, with internal consistency coefficient Cronbach's alpha 0.714. Before the interview, the interviewers gave an overview of the topic, so the participants could appreciate the basic features of medicines used in BC risk reduction.

The actual BC risk was determined by the BCRAT model on the website of the US National Cancer Center ([29]).

The BCRAT tool is one of the oldest BC risk prediction models with the most independent validations (Meads et al., 2012). It was developed in a US sample population, and then validated in further independent samples from the US population (Schonfeld, 2010) and within samples from populations of other countries such as in Germany (Hüsing, 2020), Great Britain (Amir, 2003), Czech Republic, Italy (Decarli, 2006) and Turkey (Ulusoy, 2010), i.e. countries comparable to Croatia, where the model showed adequate calibration. Therefore, although the BCRAT tool was not validated in Croatian population, it was used in our study since it was hypothesized to be applicable to Croatian women.

On the basis of calculated risk, women were classified into one of 2 risk groups - average risk and high-risk group. High-risk group of women was defined with BCRAT risk for BC in next 5 years $\geq 1.67\%$, group of average risk was defined with BCRAT risk for BC in next 5 years $< 1.67\%$. Each participant's actual BC risk was compared to her self-perceived risk and the accuracy of the BC risk self-assessment was determined. Women who incorrectly estimated their BC risk were further divided into two groups: overestimated and underestimated groups, in cases of average risk women and high-risk women incorrectly estimating their BC risk, respectively.

2.3. Statistical analysis

Categorical data were represented by absolute and relative frequencies. Numerical data were described by the median and the limits of the interquartile range. Differences of categorical variables were tested by Chi-square test and, if necessary, by Fisher's exact test. The normality of the distribution of numerical variables was tested by the Shapiro-Wilk

test. Differences between two independent groups were tested by Mann-Whitney's *U* test. Differences in numerical variables in cases of 3 and more groups were tested by Kruskal-Wallis test. The significance level was set to Alpha = 0.05. MedCalc Statistical Software version 19.1.7 (MedCalc Software Ltd, Ostend, Belgium; <https://www.medcalc.org>; 2020) was used for statistical analysis.

3. Results

3.1. Women's demographic characteristics and comparison of absolute BC self-assessment and objective BC risk

Total of 258 subjects were included in this cross-sectional study, median age 58 years (IQR 46–62 years). Eighteen subjects were excluded from the study because of incomplete data from which BCRAT risk could not be calculated. As expected, high-risk women were older, and had significantly more family members with BC, and first-degree relatives with any type of cancer in their family. Most of the subjects were menopausal with a median of two live births. More than half of women (52%) suffer from some chronic illness for which daily therapy is required, less than a quarter smoke cigarettes, and only 1% consume alcohol regularly. Majority of women had high school diploma (60%) with only 19% with master's degree or higher. With regards to the employment status, 36% of the participants were retired at the time of enrolment in the study and 30% were working in the public sector (Table 1).

The absolute self-perceived risk in the succeeding 5 years was defined as correct ($n = 170$) if a participant with BCRAT BC risk $< 1.67\%$ answered "very low", "low" or "average" in the succeeding 5 years ($n = 152$), or if a participant with BCRAT BC risk in the succeeding 5 years $\geq 1.67\%$ responded with "high" or "very high" ($n = 18$).

The absolute risk self-assessment in the succeeding 5 years was defined as underestimate ($n = 47$) if a participant with BCRAT risk for BC $\geq 1.67\%$ answered "very low", "low" or "average".

The absolute risk self-assessment in the succeeding 5 years was defined as overestimated ($n = 23$) if a participant with BCRAT BC risk $< 1.67\%$ responded with a "high" or "very high" in the succeeding 5 years.

In the group of women with average risk for BC, the majority of women gave an accurate self-assessment of their risk (87%), while in the group of high-risk women, most of women underestimated their risk (72%, χ^2 test, $p < 0.001$) as shown in Table 1.

Twenty-three participants inaccurately estimated their own BC risk higher in the succeeding 5 years with median 4 (IQR 4–4) grade (Kruskal Wallis test, $p < 0.001$) and their own lifetime risk with median 4 (IQR 4–5) grade (Kruskal Wallis test, $p < 0.001$). The same group also graded their own lifetime BC risk and BC risk in the succeeding 5 years higher when asked to compare them to BC risk of women of the same age with median 4 (IQR 3–4) (Kruskal Wallis test, $p < 0.001$), respectively (Table 2). However, these subjects were not significantly more worried about the possibility of developing BC as compared to the other participants, respectively. Participants' concerns about BC were similar in all groups, with a median grade of 3, with the answer "my worries about BC are moderate" (Table 2).

Interestingly, participants who underestimated their own BC risk had significantly more first-degree relatives with any cancer, as well as with BC in the first-degree relatives and in wider family (χ^2 test, $p = 0.02$, $p = 0.002$). These women were also significantly older (Kruskal Wallis test, $p < 0.001$) and were less likely to have an active menstrual cycle (Fisher's exact test, $p = 0.01$) as shown in Table 3. Considering the level of education and employment status, there were no significant differences between the groups. Also, there were no differences between the groups considering the number of children, as well the influence of lifestyle (chronic therapy use, cigarette smoking, alcohol consumption; data not shown).

Table 1
Women's Demographic Characteristics and Comparison of Absolute BC Risk Self-assessment in Succeeding 5 Years and Objective BC Risk.

Objective BC risk according to BCRAT model	Average BC risk (n = 175)	High BC risk (n = 65)	Total (n = 240)	P
Age (Median (25%–75%))	56 (43–61)	62 (55–66)	58 (46–62)	<0.001 [§]
Live birth (Median (25%–75%))	2 (1–2)	2 (1–2)	2 (1–2)	0.10 [§]
Education status [n (%)]				
Primary School Diploma	23 (13.1)	10 (15.4)	33 (13.8)	0.64 [†]
High School Diploma	107 (61.1)	37 (56.9)	144 (60)	
Bachelor's Degree	10 (5.7)	7 (10.8)	17 (7.1)	
Master's Degree	34 (19.4)	11 (16.9)	45 (18.8)	
Doctorate	1 (0.6)	0	1 (0.4)	
Work status [n (%)]				
Pupil	1 (0.6)	0	1 (0.4)	0.05 [†]
Student	1 (0.6)	0	1 (0.4)	
Private Sector Employee	31 (17.7)	6 (9.2)	37 (15.4)	
Public Sector Employee	57 (32.6)	17 (26.2)	74 (30.8)	
Free profession	1 (0.6)	1 (1.5)	2 (0.8)	
Unemployed	30 (17.1)	7 (10.8)	37 (15.4)	
Retired	54 (30.9)	34 (52.3)	88 (36.7)	
Any type of cancer in first degree relative [n (%)]	78 (45)	46 (72)	124 (52)	<0.001*
Family history of BC [n (%)]	20 (11)	22 (34)	42 (18)	<0.001*
An active menstrual cycle [n (%)]	60 (34)	8 (12)	68 (28)	0.001*
Suffers from chronic illness for which daily therapy is required [n (%)]	88 (50)	37 (57)	125 (52)	0.39*
Cigarette smoker [n (%)]	40 (23)	15 (23)	55 (23)	>0.99*
Regularly consumes alcoholic beverages** [n (%)]	3 (2)	0	3 (1)	0.57 [†]
Absolute self-assessment risk in succeeding 5 years [n (%)]				
Very low risk	28 (16)	10 (15)	38 (16)	0.02
Low risk	54 (31)	9 (14)	63 (26)	
Average risk	70 (40)	28 (43)	98 (41)	
High risk	19 (11)	15 (23)	34 (14)	
Very high risk	4 (2)	3 (5)	7 (3)	
Correct estimation of BC risk	152 (87)	18 (28)	170 (70)	
Incorrect estimation of BC risk	23 (13)	47 (72)	70 (30)	<0.001 [†]

* χ^2 test; [†]Fisher's Exact test; [§]Mann Whitney U test.

**Equivalent to 2dcl alcoholic beverage per day.

3.2. Knowledge about BC risk factors

Knowledge about BC risk factors was evaluated through 16 questions. The median of correct answers was 8 (with an interquartile range

Table 2
Comparison of Self-assessed Estimates of BC Risks, Self-assessed Estimates of Worry about BC Development, and Accuracy of BC Risk Self-assessment.

	Underestimated group (n = 47)	Correct estimation (n = 170)	Overestimated group (n = 23)	Total (n = 240)	P*
<i>My risk of breast cancer</i>					
In the succeeding 5 years	3 (2–3)	3 (2–3)	4 (4–4)	3 (2–3)	<0.001
Lifetime	3 (2–3)	3 (2–3)	4 (4–5)	3 (2–3)	<0.001
<i>My risk of breast cancer in comparison to BC risk of women of the same age</i>					
In the succeeding 5 years	3 (2–3)	3 (2–3)	4 (3–4)	3 (2–3)	<0.001
Lifetime	3 (2–3)	3 (2–3)	4 (3–4)	3 (2–3)	<0.001
<i>**Breast cancer worry</i>					
In the succeeding 5 years	3 (1–3)	3 (2–3)	3 (2–4)	3 (2–3)	0.29
Lifetime	3 (1–4)	3 (2–4)	3 (1.8–4.3)	3 (2–4)	0.34

*Kruskal Wallis test; Data are presented as medians (IQR 25%–75%) of grades 1 to 5.

**-1-I am not worried at all, 2-my worries about BC are small, 3-my worries about BC are moderate, 4- my worries about BC are big, 5- my worries about BC are very big.

[†] 1-very low, 2-low, 3-average, 4-high, 5-very high.

of 6 to 10 correct answers) and absolute range from only 1 to 15 correct answers. In all groups of participants, the most widely known risk factor was the first-degree relationship with a person who had BC (mother, sister, daughter) which was accurately recognized by 85% of participants (Fig. 2., Panel A, 6th row). Women who gave an accurate BC risk self-assessment were significantly more aware that being overweight is a BC risk factor (Fig. 2. Panel A, 11th row, χ^2 test, $p = 0.03$). There were no other significant differences in the correct answers with respect to BC self-assessment. However, early age at first menstruation and late menopause as risk factors for BC were recognized in only 24% and 26% of participants, respectively (Fig. 2, Panel A, second and third row).

However, results were slightly different depending on whether participants came for a scheduled diagnostic examination or to have a screening mammography (as part of National screening program). Participants who underwent screening mammography were significantly more aware that late menopause (34% vs. 21%, χ^2 test, $p = 0.03$), older age at first child birth (47% vs. 29%, χ^2 test, $p = 0.003$) and hereditary gene mutations (82% vs. 68%, χ^2 test, $p = 0.003$), were risk factors for BC, while participants who were referred for diagnostic examination were more aware that taking hormone replacement therapy after menopause is significant BC risk factor (63% vs. 46%, χ^2 test, $p = 0.009$) as presented in Fig. 2, Panel B.

3.3. Knowledge and attitudes towards BC chemoprevention

Only 43 (18%) participants had previously heard about the possibility of preventing BC by taking medication (data not shown). Subjects who had accurately assessed their risk regularly took fewer over-the-counter medications, and were significantly more familiar with the names of the chemopreventive drugs Nolvadex and Femara (Table 4).

The median of answers about the knowledge of the name, use, and side effects of hormonal therapy in all groups and for all drugs were extremely low (corresponding to answer 1 - No, I have never heard of this drug) (data not shown). The median of answers about knowledge about possibility of BC chemoprevention was also extremely low (corresponding to answer 2 - I disagree that I have heard about BC prevention with medication before) (data not shown). Surprisingly, most of participants were strongly interested in taking BC preventive therapy, with only 27 (11%) women expressing a strong disinterest and negative attitudes towards chemoprevention (data not shown).

Out of a total of 20 questions assessing attitudes toward chemoprevention, only 3 were found to be statistically significantly different between the groups with regard to the accuracy of BC risk self-assessment. Participants who accurately assessed the risk were significantly more concerned about the potential systemic and local side effects of the medication, as well as the effects on the fetus in the event of an unplanned pregnancy (Table 5).

Table 3
Association of certain, statistically significant, Demographic and Epidemiological Data with Accuracy of BC Risk Self-assessment.

	Underestimated group (n = 47)	Correct estimation (n = 170)	Overestimated group (n = 23)	Total (n = 240)	P
Any type of cancer in first degree relative [n (%)]	34 (74)	77 (45)	13 (57)	124 (52)	0.02*
Family history of BC [n (%)]	15 (32)	20 (12)	7 (30)	42 (18)	0.002*
Age (Median (25%-75%))	62 (54-67)	57 (45-61)	57 (42-63)	58 (46-62)	<0.001†
Active menstrual cycle [n (%)]	5 (11)	57 (34)	6 (26)	68 (28)	0.01‡

* χ^2 test; †Kruskal Wallis test; ‡ Fisher's exact test.

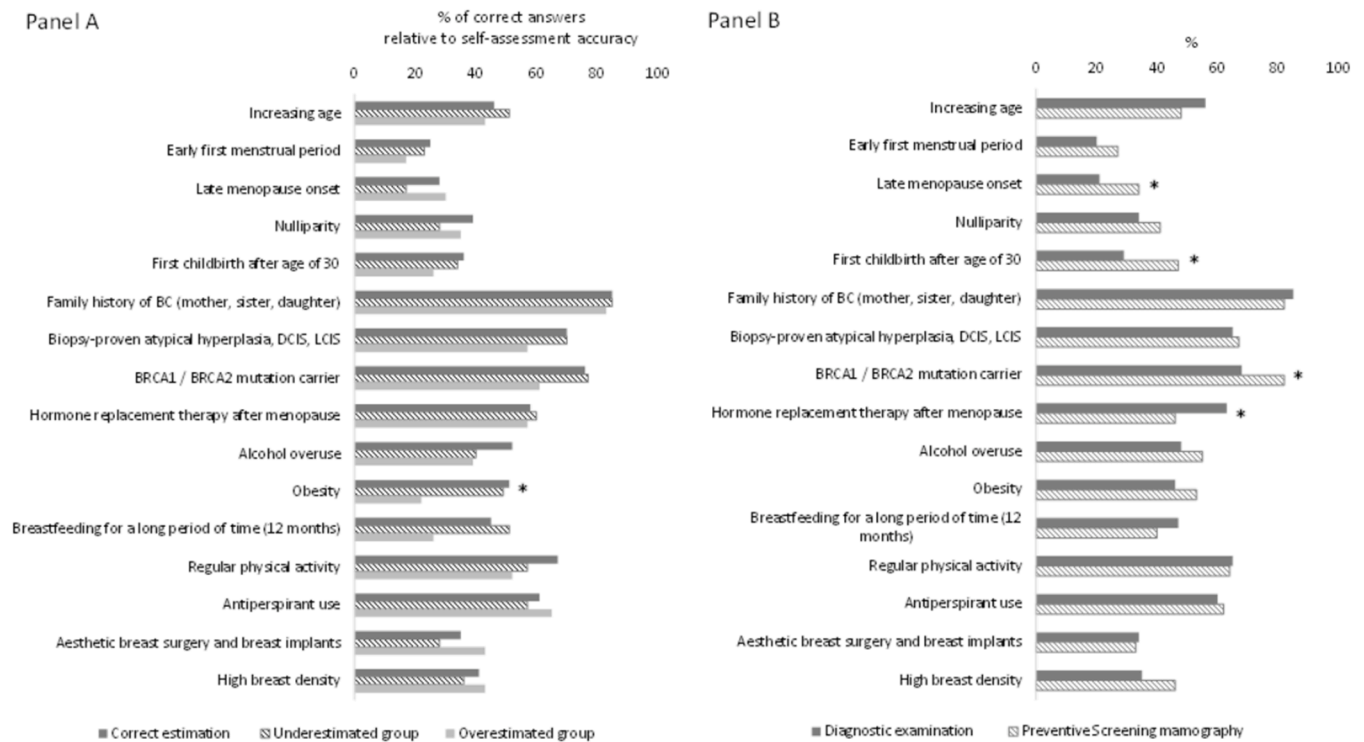


Fig. 2. Panel A; Knowledge about BC risk factors between the groups stratified according to the accuracy of BC risk self-assessment. Panel B; Knowledge about BC risk factors between the groups stratified according to the reason to attend the radiographic procedure (χ^2 test).

Table 4
Knowledge of Chemopreventive Agents According to Accuracy of Self-assessed BC Risk.

	Underestimated group (n = 47)	Correct estimation (n = 170)	Overestimated group (n = 23)	Total (n = 240)	P*
How many prescribed drugs are you taking regularly?	2 (0-2)	1 (0-2)	1 (0-3)	1 (0-2)	0.20
How many over-the-counter medications are you taking regularly?	0.5 (0-1)	0 (0-0)	0.5 (0-1)	0.5 (0-1)	0.03
I have previously heard about the possibility of preventing BC by taking medication	2 (1-3)	2 (1-3)	2 (1-3)	2 (1-3)	0.82
Have you ever heard of tamoxifen (Nolvadex)?	1 (1-1)	1.5 (1-2)	1 (1-1)	1 (1-1)	0.04
Have you ever heard of raloxifen (Evista)?	1 (1-1)	1 (1-1)	1 (1-1)	1 (1-1)	0.14
Have you ever heard of exemestane (Aromasin, Etadron, Exedrol, Peramit)?	1 (1-1)	1 (1-1)	1 (1-1)	1 (1-1)	0.06
Have you ever heard of anastrozole (Anastris, Astralis, Strazolan, Arimidex)?	1 (1-1)	1 (1-1)	1 (1-1)	1 (1-1)	0.12
Have you ever heard of letrozole (Siletris, Femara, Avomit, Letrilan)?	1 (1-1)	1.5 (1-2)	1 (1-1)	1 (1-1)	0.04

*Kruskal Wallis test; Data are presented as median (IQR 25%–75%) of grades 1 to 5 (1- no, I have never heard, 2- maybe I have heard, 3- I can recognize the name of the drug only, 4- I can recognize the name and purpose of the drug, 5- I can recognize the name, purpose and side effects of the drug).

4. Discussion

The aim of the study was to determine the BC risk perception and accuracy of BC risk self-assessment according to BCRAT model. We also

examined the factors that affect BC risk perception and their possible influence on knowledge about BC chemoprevention. Risk stratification and objective knowledge of actual BC risk is key to making a personalized approach to diagnosis and treatment. Our results showed that 78%

Table 5
Participants Attitudes towards BC Chemoprevention.

	Underestimated group (n = 46)	Correct estimation (n = 167)	Overestimated group (n = 23)	Total (n = 236)	P*
<i>Limitations of systemic BC chemoprevention</i>					
Worry about possible side effects of the drug	4 (3–4.5)	4 (4–5)	3 (2–4)	4 (3–5)	0.002
In case of unplanned pregnancy, the possible effect on the baby	1 (1–2)	1,5 (1–3)	1 (1–2)	1 (1–3)	0.04
<i>Limitations of BC chemoprevention in a form of a gel for topical use</i>					
Worry about adverse effects on the organs in the immediate vicinity of the breast (lungs, heart)	3 (2–4)	4 (3–5)	3 (1–4)	4 (3–5)	0.03

*Kruskal Wallis test; Data are presented as median (IQR 25% –75%) of grades 1 to 5 (1- I strongly disagree, 2- I disagree, 3- I neither agree nor disagree, 4- I agree, 5- I strongly agree).

of average risk, but only 28% of high risk women accurately perceived their own risk. Although most of the Croatian women perceived their BC risk accurately (71% in total), the emphasis should be on a high-risk group who mostly underestimated their risk (72%) and appear to be unrealistically optimistic. These findings are consistent with those reported in the literature data about paradoxical subsets of women unaware of their high-risk (Kartal et al., 2014; Katapodi et al., 2010; Abittan et al., 2019; Spector et al., 2009), in which primary and secondary prevention actions would be even more significant. The reasons and explanation for this optimistic bias need to be thoroughly explored in order to advance preventive behavior (Iwuji et al., 2014).

The presence of first-degree relative with BC is one of the elements in the objective assessment of BC risk. However, the results of our research are not straightforward. One third of subjects with a family history of BC underestimated their own risk (32%). These were primarily elderly women with a median age of 62 (54–67), with a high school education level, of whom 49% were retired at the time of interviewing. Many studies have also confirmed that a positive family history as a well-known BC risk factor does not actually have a significant objective impact on the risk perception (Bober et al., 2004; Hegde et al., 2018; Metcalfe et al., 2013) and not even on positive attitudes towards BC chemoprevention (Bober et al., 2004). Also, results of our research support data in the literature that older women tend to underestimate their BC risk, while younger women (<50 years of age) are more likely to overestimate their BC risk (Black et al., 1995; Graves et al., 2008; Yuksel et al., 2017). Here, we emphasize the role of physicians as well as other health professionals in raising awareness of BC risk factors and informing general population about primary and secondary prevention options.

In our study, 72% of participants were interested in taking BC chemopreventive medications, which is consistent with the literature data (Iwuji et al., 2014). The aforementioned result can be interpreted in terms of stronger motivation of the subjects who decided to participate in the research in the first place in relation to the general population. Our research confirmed that women who underwent screening mammography were also more informed about BC risk factors (Hegde et al., 2018; Graves et al., 2008). One might argue that women who underwent screening mammography were also more interested in primary chemoprevention because they were better informed. However, to the best of our knowledge, this has not been confirmed. Therefore, it would be interesting to explore attitudes towards BC chemoprevention among different cohorts of women stratified according to the reason of their visit to the doctor's office, whether they are coming to scheduled diagnostic procedure or to a preventive screening mammography, and to tailor educational and preventive actions accordingly.

With this study, we have demonstrated that Croatian women with average BC risk are not prone to taking over-the-counter drugs, and that they are significantly more concerned about the potential systemic and local side effects of the medication. Since these women have generally accurately assessed their BC risk, we hypothesize that they had a high level of health awareness, which is consistent with the literature data (Yilmazel, 2018).

Some limitations of this study include the cross-sectional structure of the study. Also, all of subjects were Caucasian, limiting the ability to generalize to the entire population. Additionally, the questionnaires were distributed in only one radiology center, representing only a subset of the general population. However, even among this population, the overall knowledge of BC and risk factors was average, and knowledge about BC chemoprevention was below average. We can assume that this knowledge would be even lower among women who do not come for regular diagnostic breast examinations or screening mammograms.

BCRAT model for personalized BC risk assessment was used in our study. Despite the fact that various models are available today, BCRAT model is the most widely studied model because it is user friendly and the findings are easy to evaluate.

The fact that we included both women referred for diagnostic ultrasound or mammography examination, and those participating in screening mammography gives strength to this study. The purpose was to evaluate the differences between the two groups and to analyze in more detail the factors which affect these differences and also affect preventive behaviors. To the best of our knowledge, this is the first study with regard to self-assessment of BC risk and knowledge about BC risk factors and about attitudes on pharmacotherapy as primary BC chemoprevention in Croatia. The data have relevance in this part of Europe, with specific characteristics in common with more advanced Western countries in which the incidence of BC is constantly increasing as a result of, among other things, lifestyles factors. Consequently, this study could help analyze various factors that would induce or distract the individual women with high BC risk from being involved in chemopreventive actions.

5. Conclusions

Personalized risk assessment significantly influenced interest in preventive behavior. We emphasize the importance of knowledge about the BC risk as critical for preventive decision-making, along with a number of other complex psychological and socio-economic factors. Given the insufficient knowledge about BC risk factors and chemopreventive modalities in our study population, the need for an additional education is highlighted in order to enhance knowledge about BC risk factors and to improve BC counseling in the affected population. Proper BC counseling has the potential to reduce worry about the disease, recommend proper time intervals and radiological screening methods to all women, recommend genetic counseling to a small selected group of women, and recommend high-risk women chemoprevention or other primary prevention methods in order to reduce BC morbidity and mortality.

Funding

This research was funded by grant from Croatian Ministry of Science and Education dedicated to multi-year institutional funding of scientific activity at the J.J. Strossmayer University of Osijek, Osijek, Croatia—grant's number: VIF-2017-MEFOS-5 (to M.S.). The APC was funded by

grant from Croatian Ministry of Science and Education dedicated to multi-year institutional funding of scientific activity at the J.J. Strossmayer University of Osijek, Faculty of Dental Medicine and Health Osijek, Croatia—grant's number: IP-2019-FDMZ-7 (to M.S.).

CRedit authorship contribution statement

Kristina Bojanic: Conceptualization, Methodology, Writing - original draft, Supervision. **Sonja Vukadin:** Data curation, Writing - original draft, Visualization. **Kaja Gragic:** Data curation. **Luka Malenica:** Data curation. **Filip Sarcevic:** Data curation. **Robert Smolic:** Methodology, Resources. **Kristina Kralik:** Formal analysis. **Aleksandar Vcev:** Project administration. **George Y. Wu:** Writing - review & editing. **Martina Smolic:** Conceptualization, Methodology, Resources, Writing - review & editing, Project administration, Funding acquisition.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

- Bray, F., Ferlay, J., Soerjomataram, I., Siegel, R.L., Torre, L.A., Jemal, A., 2018. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J. Clin.* 68, 394–424. <https://doi.org/10.3322/caac.21492>.
- Meyskens Jr., F.L., Curt, G.A., Brenner, D.E., Gordon, G., Herberman, R.B., Finn, O., Kelloff, G.J., Khleif, S.N., Sigman, C.C., Szabo, E., et al., 2011. Regulatory approval of cancer risk-reducing (chemopreventive) drugs: moving what we have learned into the clinic. *Cancer Prevention Res. (Philadelphia Pa.)* 4, 311–323. <https://doi.org/10.1158/1940-6207.CAPR-09-0014>.
- Cuzick, J., Sestak, I., Forbes, J.F., Dowsett, M., Knox, J., Cawthorn, S., Saunders, C., Roche, N., Mansel, R.E., von Minckwitz, G., et al., 2014. Anastrozole for prevention of breast cancer in high-risk postmenopausal women (IBIS-II): an international, double-blind, randomised placebo-controlled trial. *Lancet* 383, 1041–1048. [https://doi.org/10.1016/S0140-6736\(13\)62292-8](https://doi.org/10.1016/S0140-6736(13)62292-8).
- Dowsett, M., Cuzick, J., Ingle, J., Coates, A., Forbes, J., Bliss, J., Buyse, M., Baum, M., Buzzdar, A., Colleoni, M., et al., 2010. Meta-analysis of breast cancer outcomes in adjuvant trials of aromatase inhibitors versus tamoxifen. *J. Clin. Oncol.* 28, 509–518. <https://doi.org/10.1200/JCO.2009.23.1274>.
- Cuzick, J., 2018. Progress in preventive therapy for cancer: a reminiscence and personal viewpoint. *Br. J. Cancer* 118, 1155–1161. <https://doi.org/10.1038/s41416-018-0039-4>.
- Cuzick, J., Sestak, I., Cawthorn, S., Hamed, H., Holli, K., Howell, A., Forbes, J.F., 2015. Tamoxifen for prevention of breast cancer: extended long-term follow-up of the IBIS-I breast cancer prevention trial. *Lancet Oncol.* 16, 67–75. [https://doi.org/10.1016/S1470-2045\(14\)71171-4](https://doi.org/10.1016/S1470-2045(14)71171-4).
- Cuzick, J., Sestak, I., Forbes, J.F., Dowsett, M., Cawthorn, S., Mansel, R.E., Loibl, S., Bonanni, B., Evans, D.G., Howell, A., 2020. Use of anastrozole for breast cancer prevention (IBIS-II): long-term results of a randomised controlled trial. *Lancet* 395, 117–122. [https://doi.org/10.1016/S0140-6736\(19\)32955-1](https://doi.org/10.1016/S0140-6736(19)32955-1).
- Goss, P.E., Ingle, J.N., Ales-Martinez, J.E., Cheung, A.M., Chlebowski, R.T., Wactawski-Wende, J., McTiernan, A., Robbins, J., Johnson, K.C., Martin, L.W., et al., 2011. Exemestane for breast-cancer prevention in postmenopausal women. *N. Engl. J. Med.* 364, 2381–2391. <https://doi.org/10.1056/NEJMoa1103507>.
- Gail, M.H., Brinton, L.A., Byar, D.P., Corle, D.K., Green, S.B., Schairer, C., Mulvihill, J.J., 1989. Projecting individualized probabilities of developing breast cancer for white females who are being examined annually. *J. Natl. Cancer Inst.* 81, 1879–1886. <https://doi.org/10.1093/jnci/81.24.1879>.
- Costantino, J.P., Gail, M.H., Pee, D., Anderson, S., Redmond, C.K., Benichou, J., Wieand, H.S., 1999. Validation studies for models projecting the risk of invasive and total breast cancer incidence. *J. Natl. Cancer Inst.* 91, 1541–1548. <https://doi.org/10.1093/jnci/91.18.1541>.
- Reimers, L.L., Sivasubramanian, P.S., Hershman, D., Terry, M.B., Greenlee, H., Campbell, J., Kalinsky, K., Maurer, M., Jayasena, R., Sandoval, R., et al., 2015. Breast cancer chemoprevention among high-risk women and those with ductal carcinoma in situ. *Breast J.* 21, 377–386. <https://doi.org/10.1111/tbj.12418>.
- Owens, D.K., Davidson, K.W., Krist, A.H., Barry, M.J., Cabana, M., Caughey, A.B., Doubeni, C.A., Epling Jr., J.W., Kubik, M., Landefeld, C.S., et al., 2019. Medication use to reduce risk of breast cancer: US Preventive Services Task Force Recommendation Statement. *JAMA* 322, 857–867. <https://doi.org/10.1001/jama.2019.11885>.
- Ropka, M.E., Keim, J., Philbrick, J.T., 2010. Patient decisions about breast cancer chemoprevention: a systematic review and meta-analysis. *J. Clin. Oncol.* 28, 3090–3095. <https://doi.org/10.1200/jco.2009.27.8077>.
- Hackett, J., Thorneioe, R., Side, L., Wolf, M., Horne, R., Cuzick, J., Smith, S.G., 2018. Uptake of breast cancer preventive therapy in the UK: results from a multicentre prospective survey and qualitative interviews. *Breast Cancer Res. Treat* 170, 633–640. <https://doi.org/10.1007/s10549-018-4775-1>.
- Kartal, M., Ozcakar, N., Hatipoglu, S., Tan, M.N., Guldal, A.D., 2014. Breast cancer risk perceptions of Turkish women attending primary care: a cross-sectional study. *BMC Womens Health* 14, 152. <https://doi.org/10.1186/s12905-014-0152-3>.
- Park, K., Chang, S.J., Kim, H.C., Park, E.C., Lee, E.S., Nam, C.M., 2009. Big gap between risk perception for breast cancer and risk factors: nationwide survey in Korea. *Patient Educ. Couns.* 76, 113–119. <https://doi.org/10.1016/j.pec.2008.12.015>.
- Islami, F., Torre, L.A., Drope, J.M., Ward, E.M., Jemal, A., 2017. Global cancer in women: cancer control priorities. *Cancer Epidemiol. Biomarkers Prev.* 26, 458–470. <https://doi.org/10.1158/1055-9965.epi-16-0871>.
- Peltzer, K., Pengpid, S., 2014. Awareness of breast cancer risk among female university students from 24 low, middle income and emerging economy countries. *Asian Pac. J. Cancer Prev.* 15, 7875–7878. <https://doi.org/10.7314/apjcp.2014.15.18.7875>.
- Ryan, A.M., Cushen, S., Schellekens, H., Bhuachalla, E.N., Burns, L., Kenny, U., Power, D. G., 2015. Poor awareness of risk factors for cancer in Irish adults: results of a large survey and review of the literature. *Oncologist* 20, 372–378. <https://doi.org/10.1634/theoncologist.2014-0453>.
- Iwuji, C., Howells, L., Thomasset, S., Brown, K., Steward, W., Barwell, J., Thomas, A., 2014. Cancer chemoprevention: factors influencing attitudes towards chemopreventive agents in high-risk populations. *Eur. J. Cancer Prev.* 23, 594–601. <https://doi.org/10.1097/cej.0000000000000061>.
- Katapodi, M.C., Dodd, M.J., Facione, N.C., Humphreys, J.C., Lee, K.A., 2010. Why some women have an optimistic or a pessimistic bias about their breast cancer risk: experiences, heuristics, and knowledge of risk factors. *Cancer Nurs.* 33, 64–73. <https://doi.org/10.1097/NCC.0b013e3181b430f9>.
- Xie, Z., Wenger, N., Stanton, A.L., Sepucha, K., Kaplan, C., Madlensky, L., Elashoff, D., Trent, J., Petrusse, A., Johansen, L., et al., 2019. Risk estimation, anxiety, and breast cancer worry in women at risk for breast cancer: a single-arm trial of personalized risk communication. *Psychooncology* 28, 2226–2232. <https://doi.org/10.1002/pon.5211>.
- Speiser, D., Rebitschek, F.G., Feufel, M.A., Brand, H., Besch, L., Kendel, F., 2019. Accuracy in risk understanding among BRCA1/2-mutation carriers. *Patient Educ. Couns.* 102, 1925–1931. <https://doi.org/10.1016/j.pec.2019.05.007>.
- de Jonge, E.T., Vlasselaer, J., Van de Putte, G., Schobbens, J.C., 2009. The construct of breast cancer risk perception: need for a better risk communication? *Facts Views Vis. Obgyn.* 1, 122–129.
- Davids, S.L., Schapira, M.M., McAuliffe, T.L., Nattinger, A.B., 2004. Predictors of pessimistic breast cancer risk perceptions in a primary care population. *J. Gen. Intern. Med.* 19, 310–315. <https://doi.org/10.1111/j.1525-1497.2004.20801.x>.
- Alexander, N.E., Ross, J., Sumner, W., Nease Jr., R.F., Littenberg, B., 1996. The effect of an educational intervention on the perceived risk of breast cancer. *J. Gen. Intern. Med.* 11, 92–97. <https://doi.org/10.1007/bf02599584>.
- Abittan, B., Pachtman, S., Herman, S., Indelicato, J., Herman, J., 2019. Perception of Breast cancer risk in over 11,000 patients during routine mammography exam. *J. Cancer Educ.* <https://doi.org/10.1007/s13187-019-01530-5>.
- Metcalfe, K.A., Narod, S.A., 2002. Breast cancer risk perception among women who have undergone prophylactic bilateral mastectomy. *J. Natl. Cancer Inst.* 94, 1564–1569. <https://doi.org/10.1093/jnci/94.20.1564>.
- [29] National Cancer Institute, The Breast Cancer Risk Assessment Tool. Available online: <https://bcrisktool.cancer.gov/>. Accessed 02.05.2020.
- Meads, C., Ahmed, I., Riley, R.D., 2012. A systematic review of breast cancer incidence risk prediction models with meta-analysis of their performance. *Breast Cancer Res. Treat.* 132 (2), 365–377.
- Schonfeld, S.J., et al., 2010. Effect of changing breast cancer incidence rates on the calibration of the Gail model. *J. Clin. Oncol.* 28 (14), 2411–2417.
- Hüsing, A., et al., 2020. Validation of two US breast cancer risk prediction models in German women. *Cancer Causes Control* 31 (6), 525–536.
- Amir, E., et al., 2003. Evaluation of breast cancer risk assessment packages in the family history evaluation and screening programme. *J. Med. Genet.* 40 (11), 807–814.
- Decarli, A., et al., 2006. Gail model for prediction of absolute risk of invasive breast cancer: independent evaluation in the Florence-European Prospective Investigation Into Cancer and Nutrition cohort. *J. Natl. Cancer Inst.* 98 (23), 1686–1693.
- Ulusoy, C., et al., 2010. Applicability of the Gail model for breast cancer risk assessment in Turkish female population and evaluation of breastfeeding as a risk factor. *Breast Cancer Res. Treat.* 120 (2), 419–424.
- Spector, D., Mishel, M., Skinner, C.S., Deroo, L.A., Vanriper, M., Sandler, D.P., 2009. Breast cancer risk perception and lifestyle behaviors among White and Black women with a family history of the disease. *Cancer Nurs.* 32, 299–308. <https://doi.org/10.1097/NCC.0b013e31819deab0>.
- Bober, S.L., Hoke, L.A., Duda, R.B., Regan, M.M., Tung, N.M., 2004. Decision-making about tamoxifen in women at high risk for breast cancer: clinical and psychological factors. *J. Clin. Oncol.* 22, 4951–4957. <https://doi.org/10.1200/jco.2004.05.192>.
- Hegde, P., Pande, J., Adly, H.H., Shetty, P., Jayakumari, A., 2018. Breast Cancer Risk factor awareness and utilization of screening program: a cross-sectional study among women in the Northern Emirates. *Gulf J. Oncolog.* 1, 24–30.
- Metcalfe, K.A., Quan, M.L., Eisen, A., Cil, T., Sun, P., Narod, S.A., 2013. The impact of having a sister diagnosed with breast cancer on cancer-related distress and breast cancer risk perception. *Cancer* 119, 1722–1728. <https://doi.org/10.1002/cncr.27924>.
- Black, W.C., Nease Jr., R.F., Tosteson, A.N., 1995. Perceptions of breast cancer risk and screening effectiveness in women younger than 50 years of age. *J. Natl. Cancer Inst.* 87, 720–731. <https://doi.org/10.1093/jnci/87.10.720>.
- Graves, K.D., Huerter, E., Cullen, J., Kaufman, E., Sheppard, V., Luta, G., Isaacs, C., Schwartz, M.D., Mandelblatt, J., 2008. Perceived risk of breast cancer among Latinas attending community clinics: risk comprehension and relationship with

- mammography adherence. *Cancer Causes Control* 19, 1373–1382. <https://doi.org/10.1007/s10552-008-9209-7>.
- Yuksel, S., Altun Ugras, G., Cavdar, I., Bozdogan, A., Ozkan Gurdal, S., Akyolcu, N., Esencan, E., Varol Saracoglu, G., Ozmen, V., 2017. A risk assessment comparison of breast cancer and factors affected to risk perception of women in Turkey: a cross-sectional study. *Iran J. Public Health* 46, 308–317.
- Yilmazel, G., 2018. Health literacy, mammogram awareness and screening among tertiary hospital women patients. *J. Cancer Educ.* 33, 89–94. <https://doi.org/10.1007/s13187-016-1053-y>.