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ADHESION OF A GROUP OF TARGET WOMEN TO BREAST CANCER SCREENING: AN EVALUATION OF THE POSSIBLE FACTORS INVOLVED IN THE CHOICE TO BE SCREENED

A. FACCIOLÀ[1], C.E. RIZZO[1], G. VISALLI[1], R. CUFFARI[2], A. SQUERI[3], A. LAGANÀ[1,4], A. DI PIETRO[1]

[1]Department of Biomedical and Dental Sciences and Morphofunctional Imaging, University of Messina, Messina, Italy
[2]Screening Unit, Provincial Health Agency 5, Messina, Italy
[3]Medical Oncology Unit, Department of Human Pathology "G. Barresi", University of Messina, Messina, Italy
[4]Istituto Clinico Polispecialistico C.O.T., Cure Ortopediche Traumatologiche s.p.a., Messina, Italy;

Corresponding Author
Antonio Laganà, MD; e-mail: antonio.lagana1@studenti.unime.it

ABSTRACT – ***Objective:*** To understand the adhesion rate and the features of women adherent to breast cancer (BC) screening test, an essential secondary prevention tool in early diagnosis and mortality reduction.

Participants and Methods: We evaluated the adhesion of a group of target women aged 50-69, living in the provincial territory of Messina, Italy, in the five-year period 2018-2022. Specifically, we calculated the adhesion and the positivity rate through the analyses of electronic registries of the local Provincial Health Agency. Then, we investigated some features of the adherent women in order to understand which factors could be involved in the attitude to be screened. In particular, the counselling forms filled during the screening were examined and data about some well-known risk factors such as age, familiarity, number of children and breastfeeding were evaluated.

Results: The overall adhesion rate was very poor (24.5% of the invited women) with a mean positivity rate (i.e. confirmed BC) of 8%. Especially in the group of older women we detected the lower adhesion rate (18.6%). A high percentage (28%) of screened women declared a familiarity for BC. BC positivity was directly associated with age and familiarity, and inversely with number of children and breastfeeding.

Conclusions: Our findings suggest that familiarity for BC is the major motivation to be screened, especially for women with a certain awareness to be at risk; indeed, they are more inclined to adhere to mammogram screening. A strengthening of women's awareness about all the protective and risk factors for the BC development through mass media and the involvement of healthcare professionals could improve the situation, increasing the compliance to screening campaigns, especially among older women.

KEYWORDS: Screening, Mammogram, Breast cancer, Prevention.

INTRODUCTION

Breast cancer (BC) is the most common female malignancy worldwide[1-3]. In 2020, according to the World Health Organization (WHO), 2.3 million women were diagnosed with BC and 685,000 deaths occurred globally. In the same year, there were 7.8 million women alive who were diagnosed with BC in the past 5 years[4]. Incidence of this malignancy varies according to the geographical area, ranging from 27/100,000 inhabitants

in Central-Eastern Asia and Africa to 85-94/100,000 inhabitants in Australia, North America and Western Europe[5,6]. With 2.26 million new cases estimated in 2020, female BC has now become the most commonly diagnosed cancer and the most common cause of female deaths from cancer worldwide[7]. In 2020, 355,457 cases and 91,826 deaths were reported in Europe, affecting for 11.4% women aged between 20-44 years, 54% women aged between 45-69 years, and 34.6% women aged over 70 years[8]. In Italy, BC is confirmed as the most commonly diagnosed neoplasm in women, with about 55,000 new diagnoses in 2020, 12,500 deaths in 2021 and a net survival 5 years after diagnosis of 88%, with a decrease in mortality of -0,8%/year[9].

To date, we have some effective weapons for reducing the burden of this malignancy, as both primary and secondary prevention. Thanks to all the actions put in place in order to prevent and early detect BC, age-standardized mortality in high-income countries dropped by 40% between the 1980s and 2020[4]. An incidence reduction has been observed in different countries, such as the USA, Canada, Australia, and France, which have given particular importance to primary prevention in addition to an early diagnosis through the spread of screening test[7]. Primary prevention can be implemented by identifying those modifiable factors that may increase (e.g. hormone replacement therapy, ionizing radiation, menopause-dependent obesity, smoking habit and alcohol abuse) or reduce (e.g. early pregnancy, breastfeeding, physical activity) the risk of BC[10]. Secondary prevention uses screening techniques such as mammogram, echography, and magnetic resonance imaging[11]. To date, the use of digital mammogram is preferred among the other ones, because it allows a more accurate diagnosis even for women under 50 and with dense breasts[12,13]. This mammogram screening has been shown to effectively reduce mortality by 25-31% in women aged 50-69 years[14]. Echography and magnetic resonance imaging can be used as secondary diagnostic level to evaluate those cases resulted positive to the mammogram. In Italy, the 2005-2007 National Prevention Plan, included in the State-Regions Agreement of 23 March 2005, among other general purposes, provided for the strengthening of cancer screening. In November 2006, the Ministry of Health produced the "Recommendations for the planning and execution of population screening for the prevention of breast cancer, cervical cancer and colorectal cancer". Nowadays, in Italy, mammogram screening programs, activated or being implemented in most regions, provide for the execution of a mammogram every two years in women aged 50-69 years. This age group was chosen as it appears to be the one that would have the greatest net benefit from screening[15]. As reported by the last Screening National Observatory report, the positivity rates of confirmed cases to programmed screening ranged from 4.4% in 2018-2019 to 4.9% in 2020. This national picture is the average of single local situations characterised by very different regional and provincial values of adhesion and detection rates and the values in southern Italy, including the islands, were lower than the rest of the country[16].

Several risk factors for BC development are now recognized, including exogenous and endogenous (i.e. genetic) ones[17-21]. These factors are, in addition, distinguished into non-modifiable such as age and familiarity, and modifiable such as obesity, alcohol consumption, smoking habit and an increased exposure to estrogens (postmenopausal hormone replacement therapy). Among these factors, a genetic predisposition seems to play an important role since in approximately 5–10% of all BC cases, a familiar predisposition caused by germline pathogenic variants (GPVs) in various genes is recognized. This familiarity recognizes an autosomal dominant transmission[22-24]. The aim of this study was to evaluate the adhesion to the BC screening of a group of target women highlighting the features of those adherent to hypothesize which factors could be primarily involved in the attitude to undergo this essential public health tool, in order to better understand how possibly act to improve the situation.

PARTICIPANTS AND METHODS

Setting and participants

We carried out a retrospective analysis of the adhesions to BC screening campaigns carried out in the five-year period 2018-2022 in the province of Messina, Italy. Specifically, we firstly evaluated the general adhesion of the target population and then highlighted the features of the adherent women. The Messina provincial territory is healthy administered by a local Provincial Health Agency (ASP 5), which is organized into eight different districts, of which the largest one is represented by the Metropolitan city of Messina (including 37% of the entire population). All the invitations to the BC screening are annually managed by the Public Health, Epidemiology and Preventive Medicine Unit of the ASP 5 Prevention Department, which has the task to organize the screening campaigns sending the written invitations to the target population and to calculate the final data with the elaboration of annual statistics. To evaluate the adherence and the positivity percentage, the electronic registry of the ASP 5 was consulted.

According to the current Italian legislation, the target population is composed of resident women aged 50-69 years old[25]. Considering that, in Italy, BC screening is conducted every two years, each year the half of the total eligible women are invited and, specifically, that half not invited in the previous year. In addition, the undelivered invitations of the previous year and the invited women that did not undergo the exam, which are again invited as reminder, are added to this general number. Furthermore, in the final count of invitations, the women that experimented a BC in the previous 5 years and those that carried out the exam on their own at affiliated private facilities, are normally excluded from this count. These last two categories of women account on average for 25% of the eligible sample each year. Once established the real number of women to be invited per each year, written invitations are delivered through the local Postal Service. As above said, not all the send invitations are actually delivered, and a certain number of letters return to the sender. As already specified above, this number is not included in the final calculation of the adhesion.

Screening campaign

The screening campaign consists of mammograms as primary level test performed by specific diagnostic centers belonging to the local Provincial Health Agency and widespread throughout the provincial territory in order to cover the entire population. The women resulted positive to mammogram are invited to perform a secondary level test represented by a mammal echography with eventual biopsy in order to confirm and histologically characterized the lesion. Moreover, starting from 2022, a counselling about the most important risk factors is performed to all the adherent women in order to evaluate the level of risk. Specifically, a positive familiarity for BC (i.e. cases of cancer in first-degree relatives), smoking habit, hormone replacement therapy, previous pregnancies with number of children and breastfeeding, are the features put into consideration. From this counselling, we obtained information to highlight the main features of the adherent women in order to evaluate "a posteriori" which factors could have a favoring role in inducing women to be screened for BC. This evaluation was performed in all the women tested positive in 2022 and in a randomly chosen representative sample of negative women of the same year. Specifically, a systematic sampling was performed in the group of negative women in order to build our sample. We have to specify that we considered "positive" only those women that had a positive mammogram confirmed by the subsequent second level test while "negative" those women that had a negative mammogram or a positive mammogram that was not confirmed by the second level test.

Statistical analyses

Statistical analyses were performed using Prism 4.0 software (GraphPad, San Diego, CA, USA). A preliminary descriptive analysis aimed at summarizing the collected information was obtained on the samples under study. Pearson's correlation test was used to determine any correlations between the studied variables. Stratified data were statistically analyzed using χ^2 and one-way ANOVA tests. Significance was assessed at the $p < 0.05$ level.

RESULTS

In the considered five-year period 2018-2022, the territory under study had an average population value of 614,221 inhabitants, of which 92,378 women belonging to the target age group. Figure 1 shows the annual invitations, expressed as absolute number, and the trend of the adhesion percentage per each year. The figure shows that the population to which written invitations were sent was composed on average by 38,171 women, corresponding to an average invitation percentage of almost 90% of the eligible population, calculated as above said. Moreover, from the figure it is possible to notice an increasing trend of invitations overtime with a percentage increase of +22.2% between 2018 and 2022. However, the situation was different concerning the adhesion rate, which registered an average adhesion percentage of 24.5% with an irregular trend. Specifically, a particular consideration has to be made for 2020, which was the year most involved by the COVID-19 pandemic. From our analyses, it is possible to highlight that the COVID-19 pandemic did not have a negative impact on invitations, but it caused an important decrease on the adhesion rate. Indeed, after an initial improvement in 2019, with a percentage increase of +51.2% compared to 2018, the COVID-19 pandemic caused a remarkable significant decrease of -56.5% in 2020 compared to 2019 ($p = 0.0040$). A partial recovery occurred in 2021 with a remarkable significant increase of +110.3%

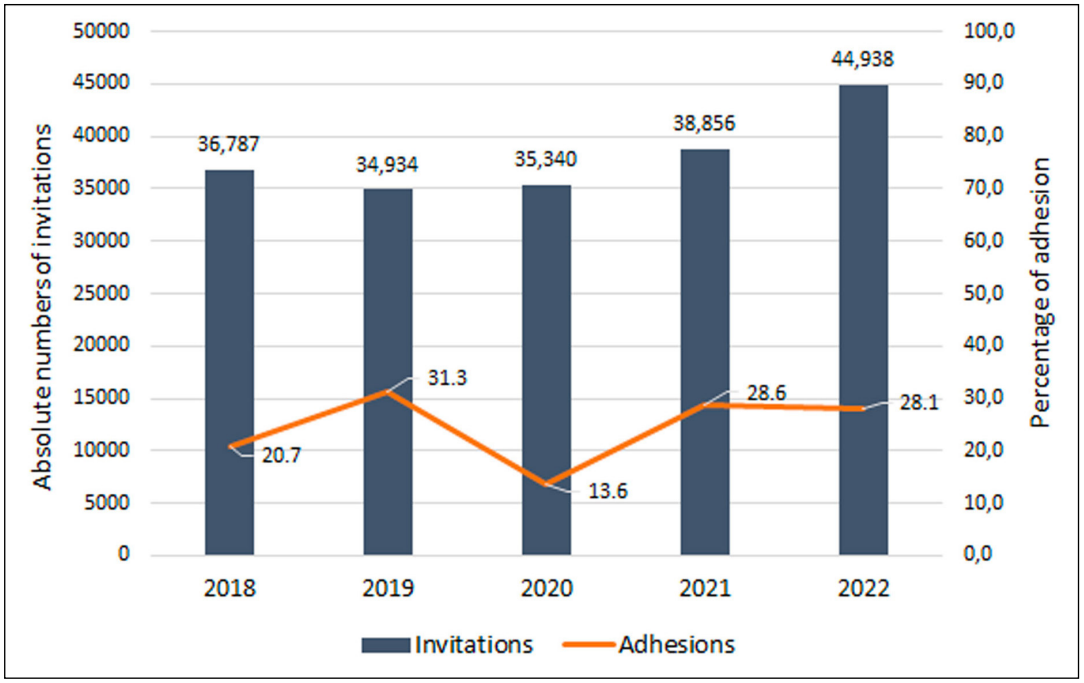

Figure 1. Trend of invitations (absolute number) and screening adhesions (percentage) in 2018-2022.

compared to 2020 (p = 0.0098), with a percentage value that is, however, slightly lower (-8.6%) than that of the immediately previous pre-pandemic year. Dividing the sample in four age groups (50-54, 55-59, 60-64, ≥65), we evaluated the different adhesion percentage values referred to the invitations in each group. The results are shown in Figure 2. From the figure, it is possible to note that the older age group (65-69) was always the less responders to the screening campaign with an average adhesion percentage of 18.6% in the five years. The average adhesion percentage of the other age groups were 24.9%, 24.9% and 23.3%, respectively. Specifically, "younger" women (50-59) had together an average adherence rate of 24.9% while only 20.9% of "older" women (60-69) adhere to invitations.

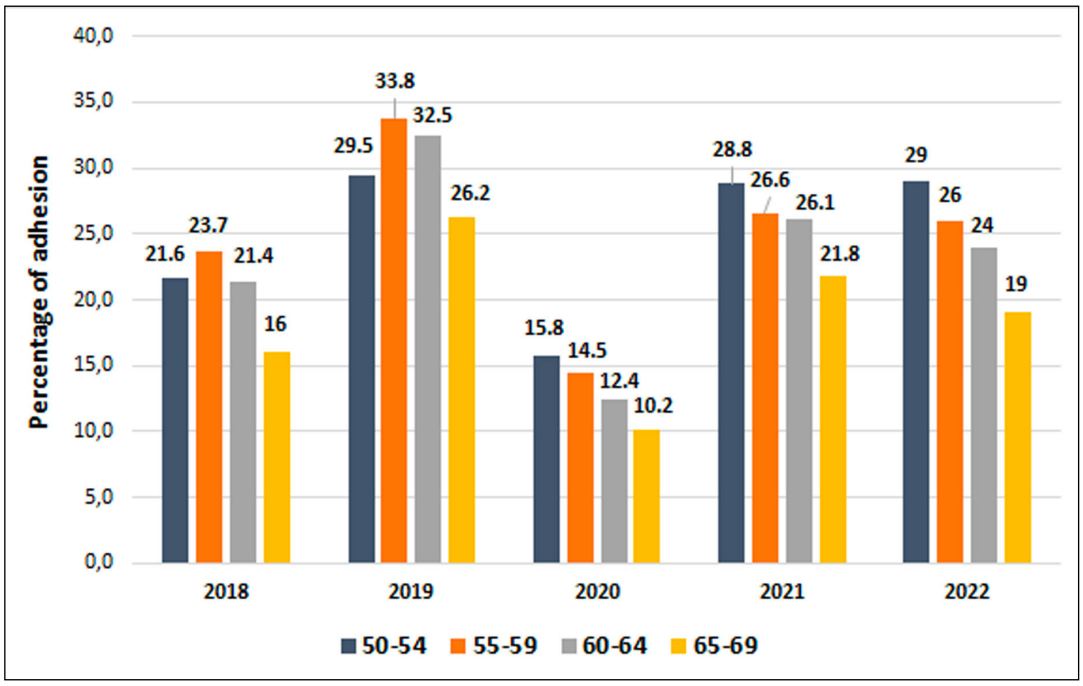

Figure 2. Percentages of mammogram screening adhesion according to the age groups of the invited women.

Finally, Table 1 shows the absolute numbers and the incidence rates of diagnosed BC (i.e. positive mammograms, later confirmed at the 2nd level tests), during the considered five-year period.

Table 1. Comparison between absolute numbers and incidence rates of confirmed positive mammograms performed in in the considered five-year period.

Year	Performed mammograms	Absolute number of confirmed positive mammograms	Incidence rates/1000
2018	7,615	67 (0.9%)	8.8
2019	10,934	85 (0.8%)	7.8
2020	4,806	49 (1.0%)	10.2
2021	11,112	79 (0.7%)	7.1
2022	12,627	99 (0.8%)	7.8
TOT	**47,094**	**379 (0.8%)**	**8.0**

The table shows that the average incidence rate was 8.0/1,000 in the considered period. The incidence rates were quite stable during the studied period, except for 2020 (the first year of pandemic) whose rate was higher and equal to 10.2/1,000 despite the number of performed mammograms was very low (-55.9% compared to the mammograms performed in 2019 and -56.7% compared to those performed in 2021). However, the positivity rate conformed to the pre-pandemic values already in the second year of pandemic when the adhesion of the invited women increased.

Once the incidence rates of confirmed cases were obtained, we estimated the number of potential cases escaped for lack of adherence considering the expected cases on all invited women based on the average positivity rate in the years 2018-20 (4‰) reported by ONS for southern Italy. These estimates are shown in Table 2. The table shows that, theoretically, a high number of cases (just over 50%) escape each year from the screening and, then, from an early diagnosis and treatment, for the lack of adhesion of the invited women and that this already critic situation was made worse by the COVID-19 pandemic, especially during the first year when the percentage of estimated escaped cases increased to 65.2% despite the highest positivity rate observed.

Table 2. Estimates of the cases escaped from early diagnosis and treatment for lack of adhesion to invitations per each year.

	Population invitation rates (%)	Adhesion rates (%)	Detected number of positive mammograms	Expected cases (4‰ positivity rate)	Estimates of escaped cases	% of estimated escaped cases
2018	93.0	20.7	67	147	80	54.4
2019	92.1	31.3	85	139	54	38.8
2020	94.4	13.6	49	141	92	65.2
2021	93.1	28.6	79	155	76	49.0
2022	94.0	28.1	99	180	81	45.0
TOT	**μ 95.1**	**μ 21.1**	**379**	**762**	**383**	**μ 50.5**

In order to confirm some of the risk and protective determinants related to the incidence of BC and to hypothesize possible determinants that could induce invited women to adhere, we evaluated the features of the women that adhered in 2022 and specifically of all those resulted positive and of an analogous group of women resulted negative. Particularly, we focused our attention on the well-known risk factors such as age, family history of BC, number of pregnancies, breastfeeding, smoking habit and

Table 3. Features of positive and negative women in 2022 according to the well-known BC risk and protective factors.

	Positive women (n=99)	Negative women (n=92)	Significance level
Mean age ± SD	59 ± 5.8	58 ± 4.8	$p = 0.0087$; R = 0.1602
Family history of BC (%)	38.3	17.6	$p = 0.0004$; OR = 3.473
Smoking habit (%)	27.8	22.6	ns
Hormonal replacement therapy (%)	23.0	15.2	ns
Pregnancies (%)	79.3	88	ns
Average number of children	1.8	2.2	$p = 0.0472$; R = -0.1481
Breastfeeding (%)	70.8	91.3	$p = 0.0005$; OR = 0.2421

use of estroprogestinic therapy. The results are shown in Table 3. The table shows that the mean age of women confirmed positive to BC was 59 ± 5.8 (min.50-max.69, that is the age range chosen by the Health Ministry for the screening) while in negative women was 58 ± 4.8 ($p < 0.01$). Concerning the positive family history for BC, a very significant difference was observed in positive women compared to the negative ones ($p < 0.001$). Moreover, no significant difference was observed in the number of women with at least one pregnancy while a significant difference was observed concerning the number of children and breastfeeding. Finally, no significant difference was found concerning smoking habit and the use of hormonal replacement therapy. Concerning age, we found a very remarkable and significant difference in the positivity percentage among the four considered age groups. The results are shown in Figure 3. The figure shows that a decreasing trend of positivity was detected with increasing age for the first three age groups. Instead, a significant increase ($p = 0.0007$) of +37.5% was found comparing the last one, which, however, showed the lowest adhesion to the screening to the mean value of the cases detected in the first three age groups.

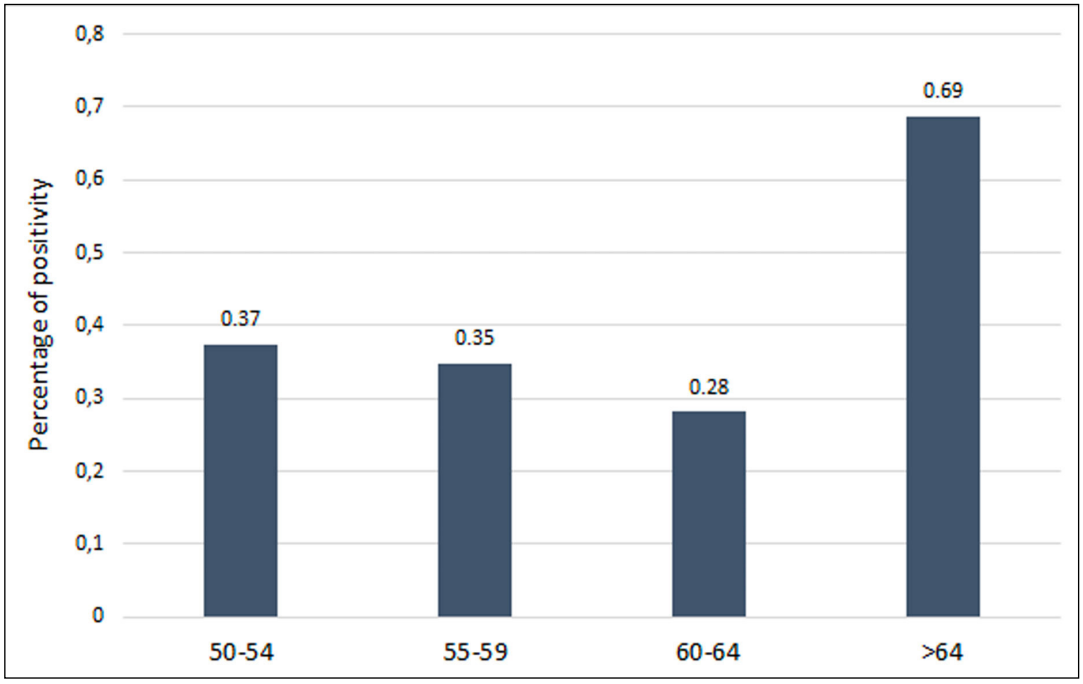

Figure 3. Positivity rate according to the four considered age groups.

DISCUSSION

BC is one of the most common malignancies worldwide and screening test is the essential secondary prevention tool to early diagnosed it and to start specific treatment as soon as possible. In Italy, according to the last Screening National Observatory report, on average about 3 million and a half women (86% of the target population) are invited through active call with an average adhesion percentage of 60% of these invited population. In 2020, in Italy the invitations decreased of 25.3% compared to the previous pre-pandemic two-year period. At the same time, the adhesion percentage decreased of almost 10% passing from 60.7% to 51% while the positivity rate was quite constant and equal to 5% in 2020[16].

Our study highlights a critical situation of mammogram screening in our territory, with percentage of adhesion much lower than the national one (24.5% *vs.* 60%) despite the very high invitation percentage of the target population. In that regard, conversely to what observed at the national level, we did not find a decrease of invitations during the first year of the COVID-19 pandemic, remaining steady the percentage in the first three considered years. Concerning adhesion, our critic situation made undoubtedly worse during the first year of the COVID-19 pandemic, when a complete lockdown from March 11th and until May 1st occurred in Italy with the stop of the main healthcare territorial activities, including cancer screenings. Our findings are in line with some previous literature researches that have shown a similar percentage decrease in mammograms adhesion especially during the first year of the pandemic[26-32]. This situation was almost completely recovered in the second year when a percentage similar to 2019 was obtained. An age difference was found in the adherence of target population, resulting the "younger" women more sensible to be screened compared to the "oldest" ones. Specifically, women belonging to the last age group were always the less sensitive and then, adherent to this essential preventive practice. Considering how the incidence remains high even in this group, this criticism highlighted by our study certainly deserves attention and has to be improved. Probably, older women are less accustomed to the culture of prevention and aware of importance to diagnose early BC. A greater involvement of this group of women it would be desirable and probably family doctors could play a leading and active role in the achievement of this purpose stressing this target group of women to positively respond to the screening campaign when they seek their medical attention for other purposes.

To explain this trend and to understand why our population is, in general, poorly inclined to adhere to a preventive practice so important in reducing the morbidity and mortality of a such widespread malignancy, we assumed that some factors could have a leading role in this attitude. To confirm this hypothesis, we decided to study some features of the women who adhered to the screening. From this evaluation, we can assume that the very low adherence value is probably linked to the fact that especially women with a positive familiar history and a higher predisposition for BC are more aware of the risk and then, more likely to be screened. This assumption is confirmed by the high familiarity value found in both positive (38.3%) and negative (17.6%) women, with an average value between the two group of 27.9%, which is the equivalent to saying that about 3 screened women out of 10 declared a familiar case of BC. This finding is remarkable higher than that reported worldwide according to which about 10% of all cases of BC are related to a genetic predisposition or family history, with differences by country and ethnicity[33]. Specifically, in Italy, a percentage of 5-7% of all the BCs has a familiar and genetic origin[34]. This partly explains the higher positivity rate found in our population compared to the national one. In fact, this positivity value of 8% is surely overestimated, being the double of that reported in Southern Italy. This assumption is also confirmed by the real incidence of BC reported in our territory in all age-group women that, in 2020, was characterized by a value of 143.3/100,000 population[35]. This burden is higher than that reported in the Sicilian Region (131.2/100,000) and that of all the Southern Italy (127.1/100,000)[7] but remarkably lower than our estimates that, on average, was 197.5/100,000 in the only target population. As above said, this result could be partly explained just from the hypothesis that especially women with a positive familiar anamnesis for BC are more sensitive to be screened and then, more likely to result positive. Essentially, we can say that there is a sort of "self-selection" of the women adherent to the screening, with the resulting bias of the very high positivity rate. This self-selection is greater in the older ones, as confirmed by the highest positivity rate observed in our sample.

As is well-known, a positive family history is one of the factor most associated with the BC onset and, in our analysis, we found that women with a positive familiarity have a more than doubled risk of developing this malignancy than women with negative screening result, in agreement with literature data[36,37]. Age was also strongly associated with the onset of BC, in line with literature data confirming that the risk for breast cancer increases with age, being about 80% of affected patients aged >50 of which more than 40% are > 65 years old[38]. Despite pregnancies were found associated with the onset of BC, we observed a negative correlation between number of children and BC positivity (the higher the

number of children, the lower the risk of BC development). Specifically, during pregnancy, hormonal changes and, especially, high levels of circulating estrogen, progesterone, IGF-1, and other growth factors are able to cause breast cell proliferation and, at the same time, could promote carcinogenesis or stimulate the progression from precancerous lesions to invasive cancer[39,40]. Moreover, the potential of estradiol and its metabolites to induce carcinogenesis in cell cultures is a well-known factor occurring during pregnancy[41]. This feature is apparently in contrast with our finding concerning the number of children. Actually, a number of research reported that one of the main risk factor for BC it would be the woman's age at pregnancy. Robertson et al[42] (1997) carried out a case-control study involving 1,248 women where they found that the woman's age at first pregnancy was associated with an annually 5.3% increase in the odds of BC development after 25 years of age. However, no effect was evidenced with the woman's age at the second or subsequent delivery. Furthermore, Albrektsen et al[43] (2005) in a large study involving 1,691,555 Norwegian women with a number of children ≤5, found an increase in the risk of BC development with increasing age at the first birth. In particular, women experienced only one pregnancy at an early age (<25 years) had always a lower risk compared to the same women with a late first age of pregnancy. These findings are perfectly in line with our results in which the number of children was inversely correlated with the risk to develop a BC, assuming that a high number of children could suggest an early age of first pregnancy. However, considering that the year of the first pregnancy is gradually increasing in Europe and especially in Italy where reached an average value of 31.3 in 2019[44], we can assume a potential parallel increasing in the BC incidence.

Finally, a very important result is the protective role highlighted in our study by breastfeeding that resulted strongly inversely related to BC risk. Based on our results, breastfeeding would seem capable to reduce the risk of BC of 76% and similar results have been showed by previous researches[45,46]. This finding is very important because, based on this results, it would be extremely useful to spread the breastfeeding "culture" in the general population stressing this remarkable positive aspect along with the others well-known benefits of breastfeeding[47,48].

CONCLUSIONS

In our geographical contexts, BC screening still suffers from a remarkable lack of adhesion, thus failing to reach its very important functions of early diagnosis and treatment. In this context, especially women with a certain awareness of the risk are more inclined to be screened and a familiarity for BC seems to be the main reason that pushes women to undergo this test and benefit of its unquestionable advantages. This situation leads to a significant loss of diagnostic and therapeutic opportunities. Despite the evident overestimations of the results due to the self-selection of our sample, our evaluation has, however, highlighted this critical situation of cases escaped from early diagnosis and treatment, which was in addition, further worsened by the COVID-19 pandemic. Actually, the pandemic caused a further reduction of the adhesion both for the complete lockdown of the period March-April 2020 and the difficulty in recovering lost mammogram tests due to the need to adapt the activity of the interested structures to the new safety standards. This side effect of pandemic was obviously observed in many other countries[49-51] and in our territory mammogram screening was completely restored in June 2020 with the active call of the women invited in March and April but unable to perform the exam. In order to improve the situation and to contrast the potential BC increase, due to due to later first pregnancies, a major involvement of all the target women is necessary. To reach this purpose, a higher engagement of health professionals such as family doctors, gynaecologists, and pharmacists, but also the diffusion of news about the importance of screening tests through mass-media and social networks could be able to increase the adhesion.

Authors contributions:

Conceptualization: A.D.P., R.C., A.F.; Data curation: G.V., A.F., A.L.; Formal analysis: A.F, G.V.; Investigation: C.E.R., A.S.; Supervision: A.D.P., R.C.; Roles/Writing - original draft: A.F., A.L., G.V.; Writing - review & editing: A.F., A.L., G.V.

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Conflict of interest:
The authors declare that they have no conflict of interest to disclose.

Ethical approval and informed consent:
Ethics approval and informed consent were not necessary due to the retrospective nature of the study. In this study, data are reported in an aggregated form, guaranteeing anonymity in accordance with the standards set forth in the Declaration of Helsinki principles of 1975, as revised in 2013.

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