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Marco Bernini, Sofia Innocenti, Daniela Turchetti, Sara Miccoli, Giovanni Innella, Alice Pellegrini, Marica Melina, Simone Zanotti, Maria Cristina Cucchi, Valentina Galluzzo, Maria Elisa Lozano Miralles, Fabrizio Ventimiglia, Daniela Cocchi & Margherita Serra

BILATERAL RISK REDUCING MASTECTOMY UPTAKE TRENDS IN HEALTHY BRCA1/2 MUTATION CARRIERS OF AN EUROPEAN CITY, THE BRACHOICE STUDY.

Marco Bernini*, Sofia Innocenti, Daniela Turchetti, Sara Miccoli**, Giovanni Innella**, Alice Pellegrini*, Marica Melina*, Simone Zanotti*, Maria Cristina Cucchi***, Valentina Galluzzo***, Maria Elisa Lozano Miralles***, Fabrizio Ventimiglia***, Daniela Cocchi****, Margherita Serra*.**

*Breast Surgery Unit, IRCCS Azienda Ospedaliero-Universitaria di Bologna

**Medical Genetics Unit, IRCCS Azienda Ospedaliero-Universitaria di Bologna

*** Breast Unit Ospedale Bellaria AUSL Bologna

**** Alma mater Studiorum Universita' di Bologna

C.A. Margherita Serra

margherita.serra@aosp.bo.it

Abstract

This study evaluates the uptake of bilateral risk-reducing mastectomy (BRRM) among unaffected BRCA1/2 mutation carriers in the metropolitan area of Bologna, Italy, between 2012 and 2024. Pathogenic BRCA variants, which confer a markedly increased lifetime risk of breast cancer, are managed through preventive strategies such as BRRM, which can reduce risk by more than 90%.

Among 178 women (89 BRCA1 and 89 BRCA2 carriers), 22.5% elected to undergo BRRM, with a significantly higher uptake among BRCA1 carriers (33.7%) compared with BRCA2 carriers (11.2%). Most procedures were performed more than two years after genetic testing, and the most common age at surgery was 41–45 years.

Furthermore, the results demonstrate a progressive increase over time in both genetic testing and BRRM uptake, in line with international trends. However, the observed rates remain lower than those reported in Northern Europe. Despite limitations related to cohort size and data completeness, this study provides updated evidence on decision-making regarding BRRM among Italian women at hereditary risk of breast cancer.

Introduction

In the 1990s, the breast cancer susceptibility genes BRCA1 and BRCA2 were identified on chromosomes 17q21 and 13q12.3, respectively. Mutations in these tumor suppressor genes occur in approximately 1 in 300–500 individuals in the general population, with prevalence varying across ethnic groups; among individuals of Ashkenazi Jewish descent, the prevalence is approximately 1 in 40.

Pathogenic variants (PVs) are inherited in an autosomal dominant pattern and represent a major risk factor for both breast and ovarian malignancies. BRCA1 and BRCA2 are classified as high-penetrance genes, with pathogenic variants conferring an estimated lifetime breast cancer risk of 72% and 69%, respectively.

Moreover, women carrying a BRCA PV tend to develop breast cancer at a younger age (mean age at diagnosis: 43 years for BRCA1 and 47 years for BRCA2) and have a higher likelihood of developing contralateral breast cancer compared with sporadic cases.

It is, therefore, essential to implement and promote dedicated programs aimed at identifying and managing women with a hereditary predisposition to breast cancer. In the Emilia-Romagna region (Northern Italy), such a program has been active since 2012, offering women carrying high-penetrance mutations the opportunity to choose among different risk management strategies.

Among available options, bilateral risk-reducing mastectomy (BRRM) represents the most effective preventive measure, decreasing the risk of developing breast cancer by at least 90%. Furthermore, BRRM may reduce anxiety related to cancer occurrence, while still guaranteeing an adequate psychological and sexual well-being, particularly when combined with immediate breast reconstruction. However, BRRM is an invasive and irreversible intervention that does not completely eliminate cancer risk and may be associated with surgical complications. For these reasons, a thorough evaluation of risks and benefits by both patients and clinicians is essential before any decision .

An international cohort study by Metcalfe et al. reported an overall BRRM uptake rate of 27.8%, with a higher propensity for surgery among women tested after 2009. The uptake of BRRM varies considerably across countries, with the highest rates observed in the United States, China, Canada, Norway, and the United Kingdom. Notably, the study included only a small Italian cohort of ten women, with data limited to the period prior to 2009.

To date , no more recent studies have specifically addressed the uptake of BRRM among unaffected BRCA1/2 mutation carriers in Italy and Southern Europe.

The present study stems from the BRACHOICE project, involving two metropolitan Breast Units, and aims to investigate the uptake of bilateral risk-reducing mastectomy (BRRM), as well as the age at surgery and the time interval between genetic testing and surgical intervention, among

Materials and methods

Study setting

We conducted a cross-sectional observational study to assess the incident performance of BRRM in BRCA mutation carriers in the urban area of Bologna. The study retrospectively considers a 12-year period from January 1st, 2012 to December 10th, 2024 and involves ~~the~~ two different Breast Units operating in the same metropolitan area.

The first collected data, regarding women diagnosed with a BRCA1/2 PV, were retrieved from the database of the Genetics Department of Bologna University Hospital, which serves as one of the four regional hub centers for mutation testing.

Hence, we collected clinical records about the PV mutation carriers to track down those who were submitted to BRRM in one of the two urban Breast Units, including age, type of genetic mutation (BRCA1 or BRCA2), date of genetic diagnosis, date and type of surgery.

The BRACHOICE Project was previously approved by the Institutional Ethical Committee of the Hospitals involved. The primary endpoint of the study was the rate of BRRM among all the BRCA1/2 mutation carriers. Secondary endpoints included evaluation of age ranges at surgery and months elapsed between genetic diagnosis and BRRM.

Study population

Women aged 18 years old or older who tested positive for a BRCA1/2 PV between January 1st, 2012 and December 10th, 2024 were included in the study. The Unit of Medical Genetics of Bologna University Hospital did not provide data regarding women who were affected by breast cancer or had a previous diagnosis of breast cancer at the time of testing. Since the study aimed to assess the choice of risk reducing bilateral mastectomy in otherwise healthy women, breast cancer affected women or previously affected women were therefore identified and excluded from the study. Moreover, women carriers of different mutations predisposing to hereditary breast cancer were excluded. Besides, some women tested by the Unit of Medical Genetics in Bologna, eventually, chose to receive follow-up care, including even surgery, at other institutes elsewhere and were also excluded due to a lack of available information.

Statistical analysis

Descriptive statistics were used for the analysis, with results presented as frequencies and proportions. A two-proportion z-test was performed to assess the statistical difference in the choice of BRRM between the BRCA1 and BRCA2 groups. Statistical significance is established for $p < 0,05$. Age at surgery is presented as 5-year intervals, except for the initial range of 25-30

years, which spans 6 years, covering ages from 25 to 70. To examine the choice of surgery in relation to different life stages, three further age groups at surgery were defined: 25-40, 41-55 and 56-70 years. Time interval between genetic testing and surgery is categorized into four different month ranges: 0-6, 7-12, 13-24 and > 24. All statistical analyses were conducted using Excel version 16.37.

Supplemental Materials: **Data are avaible on Zenodo https://doi.org/10.5281/zenodo.17896935**

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Results

Two-hundred eighty-four women tested positive for a breast cancer predisposing mutation at the Unit of Medical Genetics between January 1st, 2012 and December 10th, 2024, without any concurrent or previous breast cancer diagnosis. Thirteen of them presented a mutation of a gene different from BRCA1 or BRCA2. Ninety-three women decided to be followed by other institutes and were therefore excluded. Study cohort counts one hundred seventy-eight unaffected women (*Figure 1*), 89 (50%) carriers of a BRCA1 PV~~s~~ and 89 (50%) carriers of a BRCA2 PV~~s~~. The even distribution registered is purely incidental.

The global uptake of surgery is 22,5%, 40 out of 178 women, 75% of them were BRCA1 mutation carriers and 25% BRCA2 mutation carriers. We considered two groups: BRCA1 mutation carriers and BRCA2 mutation carriers. In the former, 33,7% (30 out of 89) chose the RRM option, while in the latter one only 11,2% (10 out of 89) chose RRM, with a statistical difference between the two groups (p=0,0003) (*Table 1*).

Figure 1: study population selection

Table 1: uptake of RRM

We analyzed the frequencies of genetic diagnoses and surgeries for each year.

The years with the highest rates of diagnosis were 2024 (14,6%), 2022 (14,0%) and 2019 (12,4%). In contrast, the years 2012 (0,6%), 2013 (1,7%), 2015 (2,2%), and 2020 (3,9%) recorded the lowest numbers of genetic tests, each accounting for less than 5% of all diagnoses. The remaining years had relative frequencies of genetic diagnoses ranging between 6.2% and 9,6% (Table 2-3).

Table 2: number and relative frequency of genetic diagnoses per year

Table 3: histogram of relative frequencies of genetic diagnoses per year

None of the women of the study cohort underwent surgery in 2012, 2013 or 2014. Surgical records begin in 2015 (2,5%). From 2016 and 2021, RRM annual rates ranged between 5% and 7,5%. Higher frequencies were observed in 2022 (15%), 2023 (25%) and 2024 (17,5%) (*Table 4-5*).

Table 4: number and relative frequencies of RRM per year

Table 5: histogram of relative frequencies of RRM per year

Among women who chose RRM, 47,5% underwent surgery more than 24 months after genetic testing, 20% between 13 and 24 months, 30% between 7 to 12 months and 0,5% within the first 6 months (*Table 6*).

Table 6: months elapsed between genetic testing and surgery presented as four ranges. Data are presented as number of women and relative frequencies

The cohort consisted of women aged between 25 and 70 years at the time of RRM. The distribution of frequencies by age group showed that 15% were aged 25 to 30, 10% were between 31 and 35, 12,5% were in the 36 to 40 age range. The modal age group was 41 to 45, representing 20% of the women who underwent surgery. Women aged 46 to 50 accounted for 15%, while those between 51 and 55 made up 10%. The 56 to 60 age group represented 12,5%, and the groups 61 to 65 and 66 to 70 each accounted for 2,5% (*Table 7*).

Table 7: number and relative frequencies of RRM for each age group

Of the forty women who choose RRM, fifteen (twelve BRCA1 and three BRCA2) were between 25 and 40 years old at the date of surgery, representing 37,5%. Eighteen women (fourteen BRCA1 and four BRCA2) were aged between 41 and 55 years old, accounting for 45% (modal class); seven women (four BRCA1 and three BRCA2) were between 56 and 70 years old, making up 17,5% (*Table 8*) .

Table 8: age group at the time of surgery, divided by mutation (BRCA1/BRCA2) and total (number and percentage)

Only 13 out of 40 patients underwent prophylactic salpingo-oophorectomy performed in the same surgical procedure together with bilateral RRM ~~.~~ All the others underwent salpingo-oopphorectomy at a different time.

All patients underwent immediate breast reconstruction (2 DIEP 26 prepectoral prostheses and 10 submuscular expanders, with the exception of two cases in which reconstruction was declined at the patients' request.

On definitive histopathological examination of the surgical specimens, occult carcinoma not detected on preoperative assessment was identified in two cases: in one case~~,~~ a focus of triple-negative invasive carcinoma of no special type (NST), and in the second case~~,~~ ductal carcinoma in situ (DCIS). No cases of ovarian carcinoma were identified in the 13 patients submitted to simultaneous salpingo-oophorectomy.

Discussion

The results show an uptake of Risk-Reducing Mastectomy (RRM) of 22.5% among all the patients carrying a BRCA mutation of the study cohort, which is similar to the rates observed in Slovenia[17] and Austria[18]. This rate is higher than those registered in France[19] and Poland[16] but lower than in other leading European countries such as England[20], Norway[21], and the Netherlands[22].

Although the cohort size is not very large, it is bigger than the Italian cohort reported in the *Metcalfe et al.* study[16] (which included only 10 patients) and allows for updated data specific to Italy, where previous data were limited to years prior to 2009.

This study includes two breast surgery units from the Emilia-Romagna region in Italy, namely both from the city of Bologna. There are no other published studies regarding RRM choice in other Italian centers or regions, so the national RRM choice rate across Italy remains unknown. However, this study could represent a first step toward increasing knowledge about RRM uptake in Italy, as a national effort in creating a registry of BRCA mutation carriers as well as a registry of performed surgeries has already been expressed.

Furthermore, a significant difference was observed in the uptake of RRM between BRCA1 and BRCA2 mutation carriers (33,7% versus 11,2%). Similar differences are registered in other studies [21,23] and may be explained by the distinct characteristics of the two mutations. BRCA1 carriers face a greater cancer risk[7] and tend to develop tumors that are predominantly triple-negative breast cancers (70-90% of cases)[24]. Consequently, women with BRCA1 mutations may perceive cancer risk differently and could gain greater benefit from surgical treatment compared to BRCA2 carriers. Supporting this, a Dutch study by *Heemskerk-Gerritsen et al*. investigated breast cancer-specific survival rates among BRCA1 and BRCA2 mutation carriers who opted for RRM versus those who chose surveillance. They found lower mortality rates among BRCA1 carriers who underwent RRM compared to surveillance at age 65, whereas the difference in mortality for BRCA2 carriers was not statistically significant[22]. It is important to say that, apart from the type of mutated gene involved, the choice of surgery can be influenced by many other factors that were not considered in this study, such as familiar or personal history of cancer, pregnancy plans, marital status, social and psychological determinants[25,26].

We observed a general upward trend over the years of observation in both the number of genetic diagnoses and surgeries performed.

Regarding genetic diagnoses, an initial increase is observed when comparing the years 2013 (1,7%) and 2014 (6,2%). Considering this specific period, a potential factor contributing to this rise could be the so-called “Angelina Jolie effect”. Following the actress’ public disclosure in 2013 of her preventive bilateral mastectomy due to a BRCA1 mutation, public awareness and demand for genetic testing increased. As reported by Evans et al., this event led to an almost doubling of BRCA mutation genetic tests and an increase of inquiries for RRM in the following months[27]. While media attention could have contributed to this increase, no direct evidence confirms this hypothesis within our study. The observed trend may also reflect improved risk stratification and referral practices, broader integration of genetic testing into routine care, and reduced costs due to technological advances. More inclusive guidelines have likely increased access and eligibility, while greater public awareness and acceptance of prophylactic surgery have contributed. Additionally, multidisciplinary care pathways, improved diagnostic accuracy, and demographic factors may have further driven the increase.

From 2016 onward, the increase in diagnoses followed a generally linear pattern, with the exception of 2020, when the reduced relative frequency of diagnoses (3,9%) may be attributed to the healthcare emergency caused by SARS-CoV-2.

Within the study sample, no surgical intervention were recorded during the first three years of observation. Annual frequencies of RRM performed remained relatively stable from 2015 to 2022, increasing in 2022 (15%), 2023 (25%) and 2024 (17,5%).

The interval between genetic diagnosis and surgery exceeded two years in approximately half of the cases (47,5%), was between 13 and 24 months in 20% of cases and ranged from 7 to 12 months in 30% of cases. In a Norwegian study[21] mean time interval was 2,6 years (mean 2,3 for BRCA1 carriers and 3 years for BRCA2 carriers), while in an American population based study median time from genetic testing to surgery was of 1,1 years[26]. The data collected in this study suggest that beyond logistical timing, the decision-making process is not immediate and may partly explain, together with the lower number of genetic diagnoses in the early period, the absence of recorded surgical interventions during the initial years of observation.

The analysis of demographic data through age grouping allowed to identify the age ranges most inclined to pursue surgery; however, this method introduced a limitation in calculating the mean age at the time of RRM. Modal class at surgery time is represented by age group 41-45 years (20%), followed in frequency by age ranges 25-30 years (15%) and 46-50 years (15%).Several other studies have investigated the mean age at RRM. In Norway, the mean age was reported as 40,1 years for BRCA1 carriers and 44,6 years for BRCA2 carriers[21]; in Slovenia, the mean age was 40,2 years for patients undergoing only RRM and 43 years for those undergoing combined RRM and risk-reducing salpingo-oophorectomy (RRSO)[17]. *Metcalfe et al.* in their large study population reported mean ages of 40,7 for BRCA1 carriers and 42,4 for BRCA2 carriers[16]. Although we cannot directly compare these published data with our own results due to methodological differences, these literature findings fall within the modal age class observed in our study.

Furthermore, grouping patients into broader age categories, can offer insights into the relationship between the decision to undergo surgery and the current life stage. Among the forty women who underwent surgery, the majority choose the surgical approach before the typical age of menopause; indeed, RRM is more effective, in terms of oncological risk reduction, when performed at younger age rather than later in life[28].

This study presents certain limitations, due to the inability to calculate mean age at surgery, mean age at genetic testing and the relatively small cohort size.

Nonetheless, the results obtained are comparable with those reported in literature and contribute to update data regarding Italian population. Thus, this work represents a relevant step toward enhancing the knowledge about this subject within the national context, improving the information available for both physicians and women carriers of BRCA mutations.

Conclusions

The present study offers contemporary data on the uptake of Risk-Reducing Mastectomy (RRM) among unaffected BRCA1 and BRCA2 pathogenic variant carriers within the Bologna metropolitan area over a twelve-year period. The overall RRM rate of 22.5%, with a significantly higher prevalence among BRCA1 carriers, aligns with findings from other European cohorts and indicates a gradual increase in the adoption of preventive surgical measures in Italy.

Although limited by its retrospective design, modest sample size, and the absence of psychosocial and demographic correlations, the study provides relevant insight into national trends in hereditary breast cancer prevention. These results highlight the need for larger, multicenter investigations and the development of a centralized national registry for BRCA mutation carriers and associated preventive interventions.

In conclusion, individualized risk assessment, multidisciplinary counseling, and evidence-based decision support remain essential components in optimizing preventive care pathways for women at elevated genetic risk of breast cancer.

Conflict of interest statement: ALL AUTHORS DECLARE NO CONFLICT OF INTEREST

Declarations

Ethics approval and consent to participate: Manuscripts reporting studies involving human participants, human data or human tissue must include a statement on ethics approval and consent : IT WAS APROVED BY COMITATO ETICO AREA VASTA : 22/2025/Oss/AOUBo.
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Authors' contributions:
conception/ design of the work: Marco Bernini, Margherita Serra
acquisition, analysis of data: Sofia Innocenti
Interpretation of data: Daniela Turchetti, Sara Miccoli, Marco Bernini, Maria Cristina Cucchi
Statistical analysis: Daniela Cocchi
Drafted the work : Sofia Innocenti, Margherita Serra
Revision of the work: Giovanni Innella, Alice Pellegrini, Marica Melina, Simone Zanotti, Maria Elisa Lozano Miralles, Fabrizio Ventimiglia, Valentina Galluzzo
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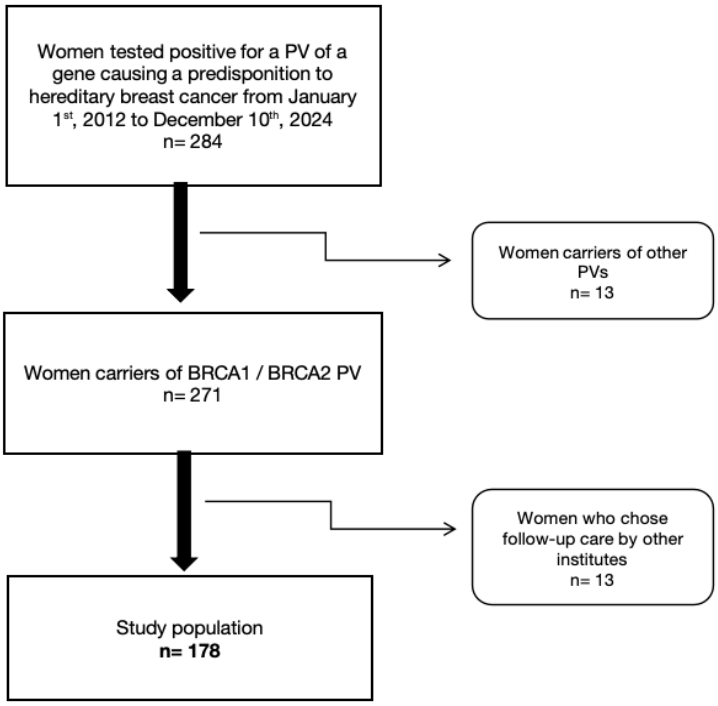

Table 1 Uptake of RRM

	Total number	RRM (number)	RRM (relative frequency)	No surgery (number)	No surgery (relative frequency)
BRCA1	89	30	0,337	59	0,663
BRCA2	89	10	0,112	79	0,888
BRCA1 + BRCA2	178	40	0,225	138	0,775

Table 2 Number and relative frequency of genetic diagnoses per year

Year of genetic testing	Number of women tested positive	Relative frequency
2012	1	0,006
2013	3	0,017
2014	11	0,062
2015	4	0,022
2016	15	0,084
2017	17	0,096
2018	15	0,084
2019	22	0,124
2020	7	0,039
2021	17	0,096
2022	25	0,140
2023	15	0,084
2024	26	0,146
total	178	1

Table 3 Histogram of relative frequencies of genetic diagnoses per year

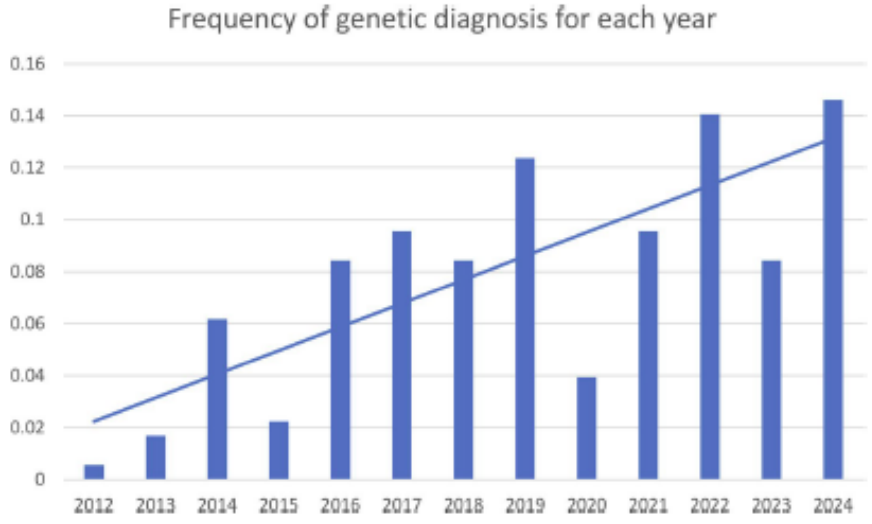

Table 4 Number and relative frequencies of RRM per year

Year of RRM	Number	Relative frequency
2015	1	0,025
2016	3	0,075
2017	3	0,075
2018	2	0,05
2019	3	0,075
2020	3	0,075
2021	2	0,05
2022	6	0,15
2023	10	0,25
2024	7	0,175
tot	40	1

Table 5 Histogram of relative frequencies of genetic diagnoses per year

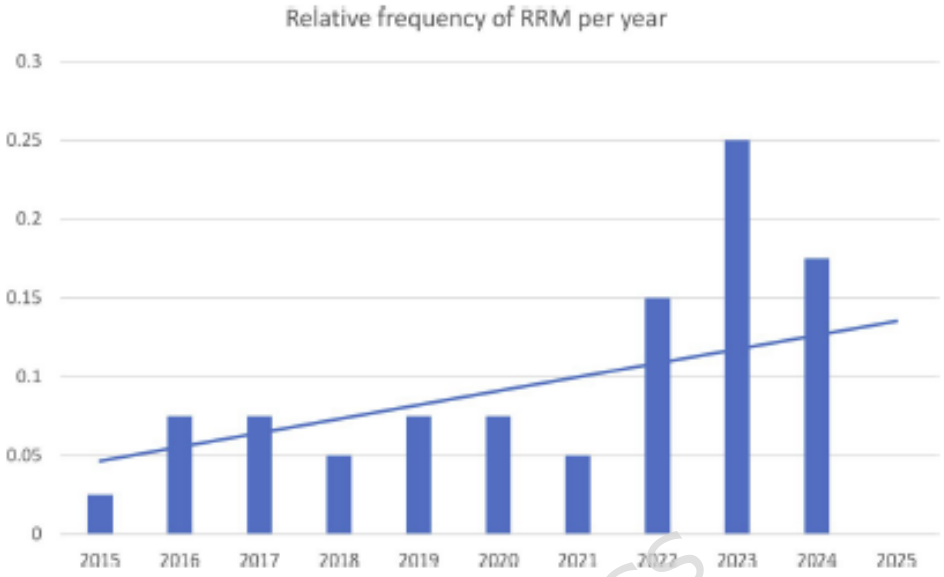

Table 6 Months elapsed between genetic testing and surgery presented as four ranges. Data are presented as number of women and relative frequencies

Month ranges	Number	Relative frequency
0-6	1	0.025
7-12	12	0.3
13-24	8	0.2
24+	19	0.475
Total	40	1

Table 7 Number and relative frequencies of RRM for each age group

Age Groups (age at RRM)	BRCA1	BRCA2	Total number (%)
Group 1 (25-40)	12	3	15 (37,5%)
Group 2 (41-55)	14	4	18 (45,0%)
Group 3 (56-70)	4	3	7 (17,5%)
Total	30	10	40

Table 8 Age group at the time of surgery, divided by mutation (BRCA1/BRCA2) and total (number and percentage)

Age ranges	Number	Relative frequency
25-30	6	0,150
31-35	4	0,100
36-40	5	0,125
41-45	8	0,200
46-50	6	0,150
51-55	4	0,100
56-60	5	0,125
61-65	1	0,025
66-70	1	0,025
tot	40	1