

## Trends and timing of risk-reducing mastectomy uptake in unaffected *BRCA1* and *BRCA2* carriers in Slovenia



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### ABSTRACT

**Objectives:** Risk-reducing mastectomy (RRM) is one of key prevention strategies in female carriers of germline *BRCA* pathogenic/likely pathogenic variants (PV/LPV). We retrospectively investigated the rate, timing and longitudinal trends of bilateral RRM uptake and the incidence and types of cancers among unaffected *BRCA* carriers who underwent genetic counseling at the Institute of Oncology Ljubljana in Slovenia.

**Materials and methods:** Female *BRCA* carriers without personal history of cancer were included in the study. Clinical data on PV/LPV type, date of RRM, type of reconstructive procedure, occult carcinoma and histopathology results was collected and analyzed.

**Results:** Of the 346 unaffected *BRCA* carriers (median age 43 years, 70% *BRCA1*, 30% *BRCA2*, median follow-up 46 months) who underwent genetic testing between October 1999 and December 2019, 25.1% had a RRM (range 35–50 years, median age at surgery 38 years). A significant difference in time to prophylactic surgery between women undergoing RRM only vs. women undergoing RRM combined with risk-reducing salpingo-oophorectomy was observed (22.6 vs 8.7 months,  $p = 0.0009$ ). We observed an upward trend in the annual uptake in line with the previously observed Angelina Jolie effect. In 5.7% of cases, occult breast cancer was detected. No women developed breast cancer after RRM. Women who did not opt for surgical prevention developed *BRCA1/2*-related cancers (9.3%).

**Conclusion:** The uptake of RRM among unaffected *BRCA* carriers is 25.1% and is similar to our neighboring countries. No women developed breast cancer after RRM while women who did not opt for surgical prevention developed *BRCA1/2* related cancers in 9.3% of cases. The reported data may provide meaningful aid for carriers when deciding on an optimal prevention strategy.

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### Introduction

Germline pathogenic/likely pathogenic variants (PV/LPV) in *BRCA1* and *BRCA2* genes are the leading genetic cause of breast and ovarian cancer. The estimated lifetime risk of breast cancer in *BRCA* PV/LPV carriers ranges from 45 to 72%. In *BRCA1* carriers, the estimated lifetime risk of breast cancer is 60–65% by age 70 years, and 72% by age 80 years. In *BRCA2* carriers, the estimated risk of breast

cancer is 45–55% by age 70 years, and 69% by age 80 years. The estimated lifetime risk of ovarian cancer ranges from 44 to 59% in *BRCA1*, and 11–17% in *BRCA2* carriers [1–3]. In Slovenia, all female *BRCA* PV/LPV carriers are encouraged to adhere to one of the two prevention strategies for breast cancer: i) intensive screening using yearly magnetic resonance imaging (MRI) of the breast combined with mammography or tomosynthesis, or ii) risk-reducing mastectomy (RRM). Risk-reducing salpingo-oophorectomy (RRSO) is also recommended for carriers between 35 and 40 years of age and upon completion of child bearing [4]. While radiological screening is less invasive and enables early cancer detection, prophylactic surgery is the only risk reducing strategy with a beneficial impact on cancer incidence and mortality. Several studies have

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demonstrated that RRM is effective in reducing the incidence of breast cancer [5–8]. RRSO has been associated with a decrease in ovarian cancer incidence and mortality [9] and a decrease in fallopian tube and primary peritoneal serous cancer incidence [8].

Several studies worldwide have investigated the uptake of RRM in *BRCA* PV/LPV carriers, which appears to be highly variable [10–20]. A recently published analysis by Metcalfe et al. noted an increase in the uptake of RRM in 2009–2017 compared to 1995–2008 [20]. Similarly, an increase in RRM rates following Angelina Jolie's public announcement on having undergone RRM in 2013 has been observed [21–23]. There is currently no available data on the rate, timing and longitudinal trends of bilateral RRM uptake in *BRCA* carriers in Slovenia. The present study aimed to assess the rate, timing and dynamics of RRM uptake among unaffected *BRCA* PV/LPV carriers in Slovenia.

## Materials and methods

### Study setting

The Cancer Genetics Clinic and the Department of Molecular Diagnostics at the Institute of Oncology Ljubljana are the central cancer genetic counseling and testing facilities in Slovenia. Since 1999, genetic counseling and testing is offered to women with personal and family history of ovarian and breast cancer. Women with confirmed *BRCA* PV/LPV and *BRCA* negative women with high breast cancer risk are assessed in a multidisciplinary setting by an onco–genetic team. In accordance with Slovenian and international guidelines, high risk women are offered risk-reducing procedures [4,24]. In Slovenia, all *BRCA* PV/LPV carriers may opt for prophylactic surgery as part of public health care service. Prophylactic surgical procedures including breast reconstruction are fully covered by the Health Insurance Institute of Slovenia and are therefore performed without additional costs for the patient. In consultation with the surgical team, patients wishing to undergo both RRM and RRSO may be offered a combined procedure.

This study was designed as a retrospective study. The rate and timing of RRM were our primary endpoints. Women who had undergone RRM and RRSO in a single (combined) procedure were also included in the analysis of the timing of RRM.

### Study population

Carriers of deleterious *BRCA1* and *BRCA2* PV/LPV who underwent genetic counseling at the Cancer Genetics Clinic at the Institute of Oncology Ljubljana between October 1999 and December 2019 and did not have a personal history of cancer at the time of genetic testing were included in the study. The National Cancer Registry of the Republic of Slovenia database was used to verify their personal history of cancer. Subjects with personal history of basal cell carcinoma, in situ melanoma, or cervical intraepithelial neoplasia were included in the study. Subjects with prior unilateral breast cancer were excluded. Subjects who were lost to follow-up or had incomplete patient records were excluded. Clinical data was retrospectively collected: age, PV/LPV type, uptake of RRM (RRM only or RRM combined with RRSO) and reconstructive procedures, date of RRM, type of reconstructive procedure, cancellation of scheduled RRM, occult carcinoma and histopathology result. Subjects who were scheduled for surgery but have not yet had the procedure, were excluded from the study. Time to prophylactic surgery (TTPS) was defined as time from disclosure of genetic test result to RRM. Follow-up was defined as time from disclosure of genetic test result to RRM for women who underwent RRM, and time from disclosure of genetic test result to the present analysis for women who did not. Annual RRM rate was calculated based on the

number of unaffected *BRCA* PV/LPV carriers who had not yet undergone RRM and/or have not been lost to follow-up.

### Statistical analysis

Descriptive statistics were used for the analysis. Categorical characteristics were presented as frequencies and proportions. Age was presented as mean, median and range. Pearson's Chi-square and the Mann-Whitney *U* test were used for statistical comparisons; a *p*-value of  $\leq 0.05$  was considered statistically significant. Poisson regression was used for time trend analysis in relation to RRM uptake. All statistical analysis was performed using SPSS v.24.0 (IBM Corp., Armonk, NY, USA).

### Ethical statement

The study was reviewed and approved by the institutional review board and Ethical Committee (consensus nr. 0110/2019) and was conducted in accordance with the Declaration of Helsinki.

## Results

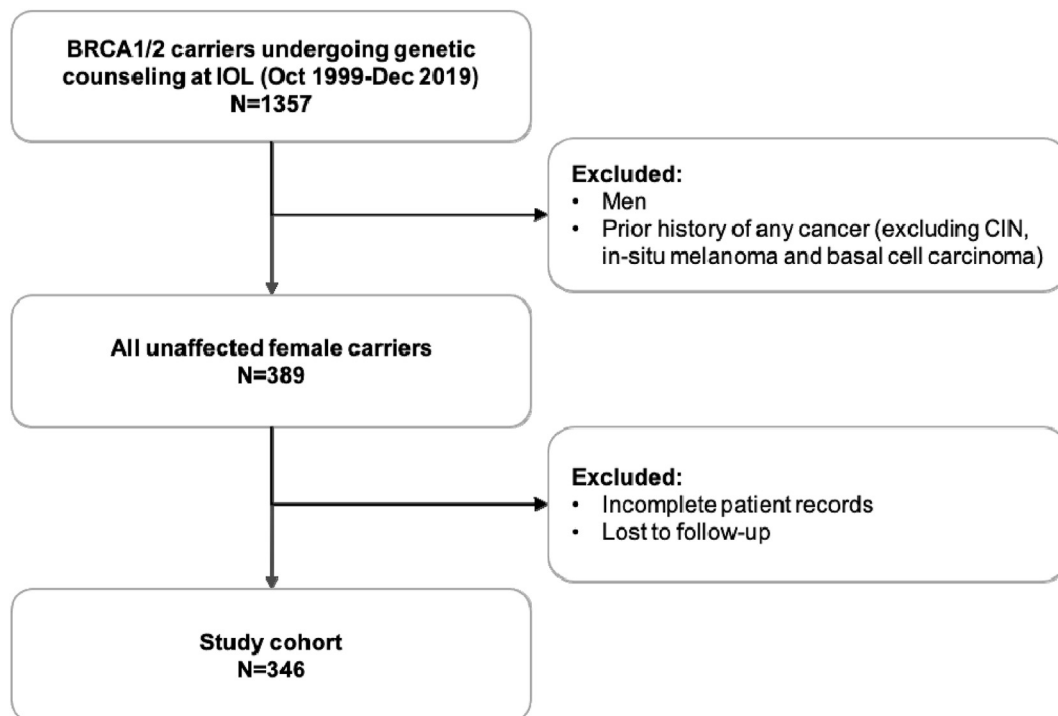
Altogether, 1357 carriers of *BRCA1* and/or *BRCA2* PV/LPV were identified in the period from October 1999 to December 2019. Men were excluded from this study since RRM is not recommended for them. Of 1177 *BRCA*-positive women, 389 had no prior history of any cancer at the time of genetic testing. 43 patients had incomplete patient records or have been lost to follow-up. One patient was scheduled for RRM, but had not yet had the procedure. Ultimately, 346 unaffected carriers met the eligibility criteria and were included in the analysis (Fig. 1, Table 1). Median time from genetic testing to disclosure of genetic test result was 2.1 months.

### Uptake of risk-reducing mastectomy

Eighty-seven (25.1%) of the unaffected *BRCA* PV/LPV carriers (74.7% *BRCA1* carriers and 25.3% *BRCA2* carriers) had undergone RRM (Table 2). Of those, 67 (77.9%) had undergone RRM only, and 20 (23.3%) had undergone a combined RRM and RRSO procedure. Median age was 37 years for women who had undergone RRM only, and 42.5 years for women who had undergone RRM with RRSO ( $p = 0.0867$ ). Median TTPS was 22.6 months for women who had RRM and 8.7 for women who had RRM with RRSO ( $p = 0.0009$ ). Eighty percent of women who had RRM only or RRM with RRSO had the surgery after July 1, 2013. Almost all women undergoing RRM had reconstructive procedures (96.6%), Table 2). Eighty-one percent of women undergoing reconstructive procedures had an implant-based reconstruction. The type of mastectomy performed (nipple-sparing mastectomy (NSM) vs. skin-sparing mastectomy (SSM)) was equally distributed. The first NSM in this population was performed in 2009. In 2013, 70% of RRM performed were SSM, whereas in 2019, only 40% were SSM and 60% were NSM. Median age at diagnosis of *BRCA* PV/LPV did not differ between the three groups.

Five patients (1.4% of unaffected carriers) had scheduled RRM, but later cancelled the procedure.

Out of 87 women who had undergone RRM, five (5.7%) were diagnosed with occult breast cancer (median age 48 years). Of those five, three were *BRCA1* PV/LPV carriers (aged 35, 48, and 62) and 2 were *BRCA2* carriers (aged 47 and 63). None of 87 developed breast cancer later on (647 person-years, median follow-up 19 months). One woman (1.1%) later developed lung cancer (age 59 years), one developed low grade endometrial stromal sarcoma (1.1%, age 47 years), and another one metastatic squamous cell cancer of unknown origin (1.1%, age 51 years).



**Fig. 1.** Flow chart illustrating the study population selection. Altogether, 346 unaffected female *BRCA1/2* pathogenic/likely pathogenic (PV/LPV carriers) were included in the study. IOL - Institute of Oncology Ljubljana; CIN - cervical intraepithelial neoplasia.

**Table 1**  
Characteristics of unaffected *BRCA* pathogenic/likely pathogenic variant (PV/LPV) carriers and patients undergoing risk-reducing mastectomy (RRM).

Characteristic	All unaffected <i>BRCA</i> carriers		No RRM		RRM	
	N = 346		N = 259		N = 87	
PV/LPV type						
<i>BRCA1</i>	242	(69.9%)	177	(68.3%)	65	(74.7%)
<i>BRCA2</i>	104	(30.1%)	82	(31.7%)	22	(25.3%)
Median age at present analysis (years)	43.0		43.0		43.0	
Mean age at present analysis (years)	44.8	(range 22–93)	44.6	(range 22–93)	45.4	(range 29–77)
Median age at PV diagnosis (years)	36.0		36.0		36.0	
Mean age at PV diagnosis (years)	38.3	(range 18–87)	38.4	(range 18–87)	37.8	(range 22–65)
Median follow-up (months) <sup>a</sup>	46.0		53.0		19.0	
Referral to testing by						
general practitioner	12	(3.5%)	4	(1.5%)	8	(9.2%)
gynaecologist	26	(7.5%)	18	(6.9%)	8	(9.2%)
oncologist	10	(2.9%)	5	(1.9%)	5	(5.7%)
other specialist	3	(0.9%)	2	(2.3%)	2	(2.3%)
relative (carrier)	272	(78.6%)	217	(84.4%)	55	(63.2%)
self	16	(4.6%)	9	(3.5%)	7	(8.0%)
other	7	(2.0%)	5	(2.0%)	2	(2.2%)

<sup>a</sup> Calculated as time from disclosure of genetic test result to RRM for women who underwent RRM, and time from disclosure of genetic test result to the present analysis for women who did not.

Out of 259 women who had not undergone RRM, 24 (9.3%) developed *BRCA1/2*-related cancers. Twelve women (4.6%, median age 38 years, range 29–65 years) developed invasive breast cancer and one (0.4%, age 40 years) developed ductal carcinoma in situ. Additionally, two women (0.7%, ages 41 and 24 years) developed cervical cancer, one (0.4%, age 40 years) developed thyroid cancer, and one (0.4%, age 66 years) developed serous endometrial cancer (*BRCA1* carrier).

Out of 259 women who had not undergone RRM, 108 (41.6%) had undergone RRSO and the remaining 151 (58.3%) women had no prophylactic procedures (RRM or RRSO). Among the 151 women who had no prophylactic procedures, five (3.3%, median age 57 years, range 50–63 years) women developed tubal carcinoma and

five women (3.3%, median age 57 years, range 35–56 years) developed ovarian cancer.

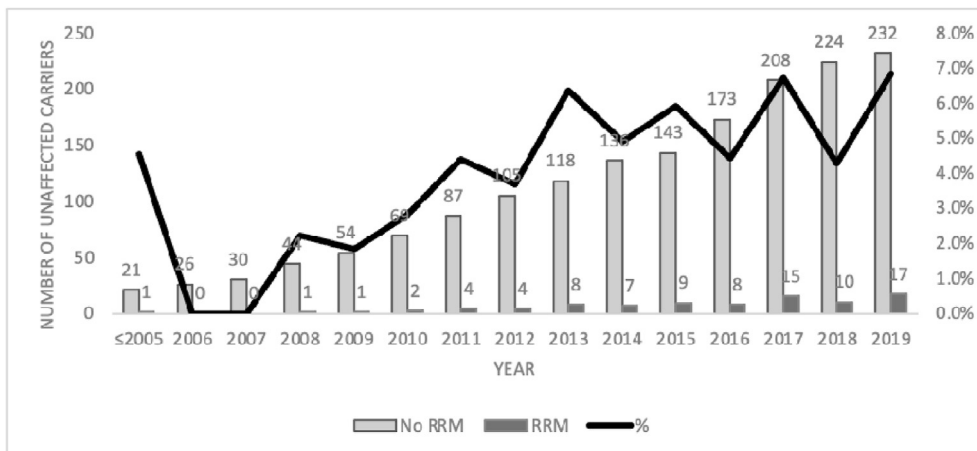
#### Dynamics of uptake of risk-reducing mastectomy

The distribution of uptake of RRM is presented in Fig. 2. An upward trend in the number of performed RRM can be observed throughout the timeline (incidence rate ratio 1.10, 95% CI 1.09–1.11;  $p < 0.001$ , Poisson regression). We noted an increase in RRM uptake starting in 2013 and rising in the following years. In 2019, 6.83% of unaffected carriers had undergone a RRM. The uptake of RRM was significantly higher in the period from July 1, 2013 to present day compared to the period before July 1, 2013 ( $p = 0.009$ ).

**Table 2**  
 Characteristics of carriers undergoing risk-reducing mastectomy (RRM) only or combined with risk-reducing salpingo-oophorectomy (RRSO).

Characteristic	RRM, any (RRM only and RRM with RRSO)		RRM only		RRM with RRSO	
	N = 87		N = 67		N = 20	
PV/LPV type						
BRCA1	65	(74.7%)	51	(76.1%)	14	(70.0%)
BRCA2	22	(25.3%)	16	(23.9%)	6	(30.0%)
Mean age at surgery (years)	40.8	(range 26–70)	40.2	(range 26–70)	43.0	(range 31–55)
Median age at surgery (years)	38.0		37.0		42.5	
Age by group						
25–29	2	(2.3%)	2	(3%)	0	(0)
30–34	15	(17.2%)	12	(17.9%)	3	(15.0%)
35–39	30	(34.5%)	25	(37.3%)	5	(25.0%)
40–49	26	(29.9%)	20	(29.9%)	6	(30.0%)
50–59	10	(11.5%)	4	(6.0%)	6	(30.0%)
>60	4	(4.6%)	4	(6.0%)	0	(0)
Median time to RRM (months)	19.7		22.6		8.7	
Period of RRM						
before July 1, 2013	17	(19.5%)	13	(19.4%)	4	(20.0%)
after July 1, 2013	70	(80.5%)	54	(80.6%)	16	(80.0%)
Occult breast cancer						
total	5	(5.7%)	4	(6.0%)	1	(5.0%)
DCIS	2	(2.3%)	1	(1.5%)	1	(5.0%)
IDC	2	(2.3%)	2	(3.0%)	0	(0)
Papillary carcinoma	1	(1.1%)	1	(1.5%)	0	(0)
Reconstructive surgery						
total	84	(96.6%)	63	(96.5%)	19	(95.0%)
autologous	14	(16.1%)	14	(20.9%)	0	(0)
implant	68	(78.2%)	49	(73.1%)	19	(95.0%)
Type of mastectomy						
nipple-sparing	44	(50.6%)	36	(53.7%)	8	(40.0%)
skin-sparing	40	(46.0%)	29	(43.3%)	11	(55.0%)
simple	3	(3.4%)	2	(3.0%)	1	(5.0%)

Legend: PV/LPV- pathogenic/likely pathogenic variant; DCIS - ductal carcinoma in-situ; IDC - invasive ductal carcinoma.



**Fig. 2.** The uptake of risk-reducing mastectomy (RRM) among unaffected BRCA carriers per year. The “no RRM” group represents all cases at risk in the corresponding year (including those from prior years who have not undergone RRM and/or have not been lost to follow-up or been diagnosed with cancer). The rate of RRM over time (expressed as %) was calculated as the number of carriers undergoing RRM each year divided by all cases at risk. An upward trend in RRM uptake can be observed (incidence rate ratio 1.10, 95% CI 1.09–1.11;  $p < 0.001$ , Poisson regression).

The distribution of median TTPS is presented in Fig. 3. TTPS was longest in carriers undergoing RRM in 2013 (36.8 months) and shortest in 2011 (8.6 months). No clear trend was observed.

**Discussion**

This study aimed to provide a longitudinal analysis of the rate and timing of RRM among unaffected BRCA PV/LPV carriers in Slovenia. This is the first study to provide Slovenian population-

specific data as well as review the incidence and types of cancers in a cohort of carriers who had not undergone RRM, and the corresponding age at which these cancers arose.

Since the establishment of genetic testing and counseling for women with relevant cancer family history in Slovenia in 1999, 87 (25.1%) unaffected BRCA carriers underwent a RRM. The uptake of RRM was slightly higher among BRCA1 carriers compared to BRCA2 carriers. The rate of RRM uptake observed in our study is in line with other published research of unaffected BRCA PV/LPV carriers

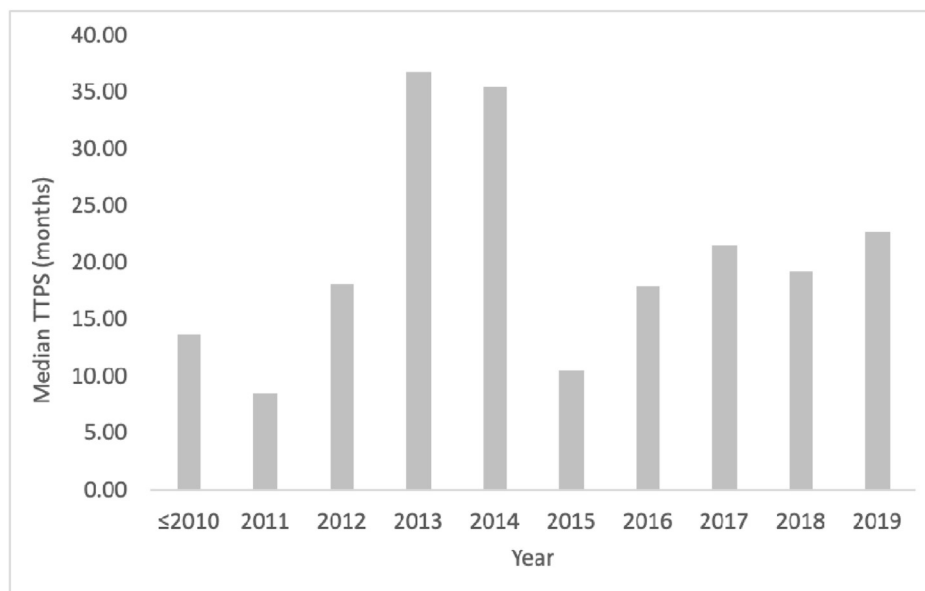


Fig. 3. The distribution of median time to prophylactic surgery (TTPS) among unaffected *BRCA* carriers.

[12,18,20]. In 2019, Metcalfe et al. reported a 27.8% RRM uptake among unaffected *BRCA* carriers from 10 countries with wide variation across studied countries [20]. The rate of uptake of RRM in unaffected Slovenian carriers is comparable to the rate of uptake in the neighboring Austria (28.2%) and higher than the rate in the neighboring Italy (10%). The rate of RRM uptake observed in our study is lower than the uptake reported by Singh et al. (42%, United States) and Evans et al. (40%, United Kingdom) [14,19]. The variability in reported rates is likely multifactorial and related to socioeconomic context. In Slovenia, prophylactic surgery is not associated with any additional costs for the patients and has been fully funded by the national health insurance since the establishment of genetic testing. We assume financial issues are not a factor in the Slovenian patients' decision for prophylactic surgery. On the other hand, women who do not opt for prophylactic surgery are offered organized and centralised high-risk screening in specially dedicated breast unit in a multidisciplinary setting with the highest expertise in public health care service. We believe the high degree of accessibility of Slovenia's organized high-risk screening units may be sufficient to create a sense of security in *BRCA* PV/LPV carriers, prompting them to decide against prophylactic surgery.

Interestingly, we observed a significant difference in TTPS between women undergoing RRM only and women undergoing RRM combined with RRSO. This could be related to the age distribution between the two groups (median age 38 vs. 42 years, 60% of women in the RRM with RRSO group were older than 40 years). However, this may also reflect the perception of risk among a certain population of women which prompts them to take more aggressive action sooner and undergo all available prophylactic procedures. We plan to investigate this further in a questionnaire-based study.

In the longitudinal analysis, we observed an upward trend in the uptake of RRM since the establishment of genetic testing. There was an increase in the number of RRM performed in 2013 and the years following. Moreover, our data shows the uptake of RRM was significantly higher in the period from July 1, 2013 to the present day compared to the period from the introduction of genetic testing to July 1, 2013. We hypothesize this may be linked to the public announcement made by the actress Angelina Jolie in May 2013 (the so-called 'Angelina Jolie effect') [22,25]. In an open editorial, the actress disclosed information about being a *BRCA1* carrier and

having undergone bilateral RRM, which created publicity worldwide [22,26]. The announcement was followed by an increase in referrals to genetic testing and inquiries into RRM [22,27], as well as an increase in the uptake of RRM [21,23,28] and RRSO [23]. Similarly to reports from other countries, we believe our data demonstrates the influence of a high profile celebrity's decision to undergo prophylactic surgery on *BRCA* carriers facing variable degrees of uncertainty or (mis)understanding about their breast cancer risk, prompting them to proceed more aggressively in diminishing this risk.

In relation to this observation, we also examined longitudinal trends in median TTPS to see if the Angelina Jolie effect may have also influenced time to decision for RRM. A spike in TTPS was noted in women undergoing RRM in the years 2013 and 2014 (36 and 35 months, respectively). Evans et al. reported similar observations. Their research 6–24 months following May 2013 shows carriers >18 months after testing positive accounted for 74% of RRM performed at that time, whereas prior to 2013 the majority of women had RRM within 18 months of testing positive [14,21]. Together with the observed increase in the number of RRM in 2013 as compared to previous years, the observed delay in decision-making appears to reflect the action of *BRCA* carriers who may have been hesitant about prophylactic surgery in the previous years to proceed more aggressively about their cancer risk.

In our studied cohort, almost all women undergoing RRM also underwent breast reconstructive procedures and of those women, 81% had implant-based reconstruction. Although implant reconstruction is generally considered the most commonly performed method of breast reconstruction [29,30], there are reports of higher uptake of autologous reconstruction in prophylactic mastectomy patients [31]. According to Bletsis et al. autologous reconstruction was also associated with a better complication profile in their patient cohort [31].

The type of mastectomy performed was equally distributed among our patient population with NSM being the predominant surgery performed in the recent years. The long-term oncological safety of both techniques is still a matter of discussion. The oncological safety of the SSM has been primarily investigated in patients with existing breast cancer and its safety is comparable to traditional non-conservative surgeries [32–34]. However, in *BRCA* PV/

LPV carriers, the oncologic outcomes have not been well-studied. The longest reported follow-up of 51 months in a cohort of 26 patients undergoing prophylactic SSM implies SSM is an oncologically safe procedure in BRCA carriers [35]. Compared to SSM, NSM conserves the nipple-areolar complex, leaving behind additional ductal tissue which may be a concern especially in patients who carry genetic mutations. In the recent years, many studies reported on the oncologic safety of the NSM in high-risk patients with median follow-up ranging from 28 to 49 months [36–38]. Despite relatively short follow-ups and retrospective nature of these reports, NSM appears to be highly preventative against breast cancer in BRCA carriers while offering superior cosmetic outcomes [37,39,40] and is as such at present the preferred option for unaffected high-risk patients in our institution.

During the course of genetic counseling, women often raise questions about their cancer burden in relation to not undergoing prophylactic surgery. We observed a 5.7% prevalence of occult breast cancer in the series of 87 consequently operated unaffected BRCA carriers. In a similar patient cohort, Collins et al. reported a 16% occult breast cancer rate [18]. A lower prevalence of occult breast cancer in our series might be the result of breast imaging performed on every woman before surgery. In the period of median 19 months of follow-up, no women developed breast cancer after prophylactic surgery. While our data are encouraging, this follow-up is very short and longer follow-up is required for reliable longitudinal assessment. After 14 years of follow-up, the reported breast cancer incidence in women with family history of breast cancer who underwent RRM is 1.4% [5].

Our study provides detailed information on the incidence and age of onset of cancers that arise in women who do not undergo prophylactic procedures. Based on the experience of our genetic clinic, this information is very relevant in the process of genetic counseling to illustrate risk and advise on the age to undergo prophylactic surgery. As expected breast, ovarian and tubal cancer were the most commonly diagnosed cancers in this population.

We also noted a high percentage of women who have been referred for genetic counseling through a relative (78%) rather than other specialists. This data implies high level of genetic testing uptake and awareness of the importance of cascade testing among the Slovenian population, most probably due to comprehensive pre- and post-testing counseling of an index case (proband).

Our study is associated with limitations due to its retrospective nature as well as the relatively small sample size and short follow-up. Although the data presented in this study provides relevant population-specific information to the process of genetic counseling, the study reflects trends in a country and the generalizability of results in other countries is questionable. On the other hand, the results presented in this study are derived from a centralised genetic testing facility and therefore provide a reliable source of information for genetic counseling and public health efforts on a national level.

## Conclusions

The uptake of prophylactic RRM among unaffected BRCA carriers in Slovenia has gradually risen over time. At 25.1%, the uptake of RRM among Slovenian unaffected carriers today is similar to our neighboring countries but lower than in northwestern Europe or the USA. In the present study, a statistically significant Angelina Jolie effect on Slovenian women's decision-making was observed. More than half of the women in our investigated cohort opted for surgery between 35 and 50 years of age, with median age at 38 years. The prevalence of 5.7% of occult breast cancer was detected. No women developed breast cancer after prophylactic surgery while women who did not opt for surgical prevention developed

BRCA1/2 related cancers in 9.3% of cases. We believe the results of this study may provide meaningful aid for Slovenian BRCA carriers when deciding on an optimal prevention strategy.

## CRedit authorship contribution statement

**Taja Ložar:** Data acquisition, Writing – original draft. **Janez Žgajnar:** Conceptualization, Methodology, Writing – review & editing. **Andraž Perhavec:** Conceptualization, Methodology. **Ana Blatnik:** Writing – review & editing. **Srdjan Novaković:** Writing – review & editing. **Mateja Krajc:** Conceptualization, Writing – review & editing, Supervision.

## 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.

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