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EPIDEMIOLOGY

Use of risk-reducing surgeries in a prospective cohort of 1,499 *BRCA1* and *BRCA2* mutation carriers

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Abstract Inherited mutations in *BRCA1* or *BRCA2* (*BRCA1/2*) confer very high risk of breast and ovarian cancers. Genetic testing and counseling can reduce risk and death from these cancers if appropriate preventive strategies are applied, including risk-reducing salpingo-oophorectomy (RRSO) or risk-reducing mastectomy (RRM). However, some women who might benefit from these interventions do not take full advantage of them. We evaluated RRSO and RRM use in a prospective cohort of 1,499 women with inherited *BRCA1/2* mutations from 20 centers who enrolled in the study without prior cancer or RRSO or RRM and were followed forward for the occurrence of these events. We estimated the age-specific usage of RRSO/RRM in this cohort using Kaplan–Meier analyses. Use of RRSO was 45 % for *BRCA1* and 34 % for *BRCA2* by age 40, and 86 % for *BRCA1* and 71 % for *BRCA2* by age 50. RRM usage was estimated to be 46 % by age 70 in both *BRCA1* and *BRCA2* carriers. *BRCA1* mutation carriers underwent RRSO more frequently than *BRCA2* mutation carriers overall, but the uptake of RRSO

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in *BRCA2* was similar after mutation testing and in women born since 1960. RRM uptake was similar for both *BRCA1* and *BRCA2*. Childbearing influenced the use of RRSO and RRM in both *BRCA1* and *BRCA2*. Uptake of RRSO is high, but some women are still diagnosed with ovarian cancer before undergoing RRSO. This suggests that research is needed to understand the optimal timing of RRSO to maximize risk reduction and limit potential adverse consequences of RRSO.

Keywords Risk reduction · BRCA1 · BRCA2 · Surgical prevention · Uptake

Introduction

BRCA1 and *BRCA2* (*BRCA1/2*) mutations confer elevated risks of developing breast and ovarian cancer [3]. Genetic testing for *BRCA1/2* mutations has value because medical decisions can be made using this information [19]. It has been well established that the use of preventive surgery can dramatically reduce cancer risks and mortality in women who carry these mutations [5–8, 13, 20]. Because there is no effective early detection for ovarian cancer that reduces mortality [15], and most ovarian tumors are detected at late (incurable) stages, it has been recommended that women undergo risk-reducing salpingo-oophorectomy (RRSO) by age 35–40 or completion of childbearing [1, 11, 18]. However, there are also long-term risks and quality of life concerns associated with premature menopause, hence women might delay timing of oophorectomy (Ref Bradbury et al.). Breast cancer early detection and preventive strategies are available for women with *BRCA1/2* mutations and women can chose between these options and risk-reducing mastectomy (RRM).

The consequences for underutilization of RRSO include elevated cancer incidence and mortality rates in women who do not undergo this surgery in a timely manner. Despite the proven effectiveness, uptake of these strategies still varies greatly and appears to be underutilized. Utilization of RRSO among *BRCA1/2* mutation carriers has been reported to be no higher than 75 % overall, 36 % in unaffected women within 5 years of genetic testing, and 49 % among breast cancer cases within 5 years of genetic testing [2, 4, 9, 10, 12, 14, 16, 17, 21, 22]. Utilization of RRM has been reported to be lower than RRSO in most studies.

While prior studies have demonstrated underutilization of RRSO and low rates RRM, they are limited in that they involved relatively small sizes, did not stratify utilization by *BRCA1* and *BRCA2* mutation carriers separately, were not prospective in nature, and did not account for concurrent events in the natural history of cancer or other forms of cancer prevention (e.g., screening mammography/MRI, SERMs, etc.). In this paper, we present the results of RRSO and RRM utilization in a large prospective cohort of women with *BRCA1/2* mutations to obtain a better estimate of cancer preventive strategies and to provide data that may help to increase appropriate utilization of these preventive options.

Methods

Participants

Women with inherited, disease-associated *BRCA1/2* mutations were identified from 20 centers of the PROSE consortium using research protocols as previously described [5, 6]. All participants underwent an informed consent process for participation in research. This protocol was approved by each institution's IRB. Study participants

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were enrolled as a cohort with time of follow-up starting from patient ascertainment into the research program. Genetic testing was performed per institutional guidelines and all patients received post-testing counseling to review medical management options. Women who declined RRSO or RRM were offered increased surveillance at all centers according to established guidelines. At US sites, this consisted of annual mammogram and annual MRI for those with breast tissue, and every 6–12 month transvaginal ultrasound and CA125 for those with ovaries in place (www.nccn.com). In the UK, women were offered yearly mammograms, as well as yearly MRI until age 50. Ovarian cancer screening consisted of transvaginal ultrasound (TVUS) and 4-monthly CA125 tests, but only as part of the UKFOCSS screening trial which stopped recruiting in 2010 [20]. Participants were eligible for the study if they had no cancer diagnosis and no RRSO/RRM at the time of ascertainment

Prospective follow-up

Usage of RRSO or RRM was the primary end-points of interest. Start of follow-up was from the age at study recruitment. For the probability of undergoing RRSO, age was right censored at the age of RRSO, RRM, diagnosis of ovarian or breast cancer, death, or the last follow-up. For the probability of using RRM, age was right centered at the time of undergoing RRM, diagnosis of ovarian or breast cancer, death, RRSO, or the last follow-up. Women were retained in the analyses if they were diagnosed with an occult ovarian cancer at RRSO.

Statistical analysis

We used Kaplan–Meier analysis to estimate the cumulative probability of undergoing RRSO and/or RRM by age, stratified on *BRCA1*/*BRCA2* carrier status, birth year (before and after year 1960), mutation testing status, or parity. A log-rank test was performed to assess the difference in the surgery uptake between strata. Similar analyses were performed to estimate rates of RRSO uptake among women who developed breast cancer. Follow-up time was accumulated from the time at breast cancer diagnosis until time at RRSO, RRM, death, or last follow-up. We also estimated RRSO uptake among women who underwent RRM. For this analysis, follow-up was accumulated from the age at RRM to the age of RRSO, ovarian cancer, death, or last follow-up. When missing data were encountered, the individual was dropped from the analysis that involved the missing data point, but the individual was included in other analyses where complete data were available. Inferences of statistical significance were made at the $P = 0.05$ level based on two-sided hypotheses. All analyses were undertaken using software R (http://www.r-project.org/).

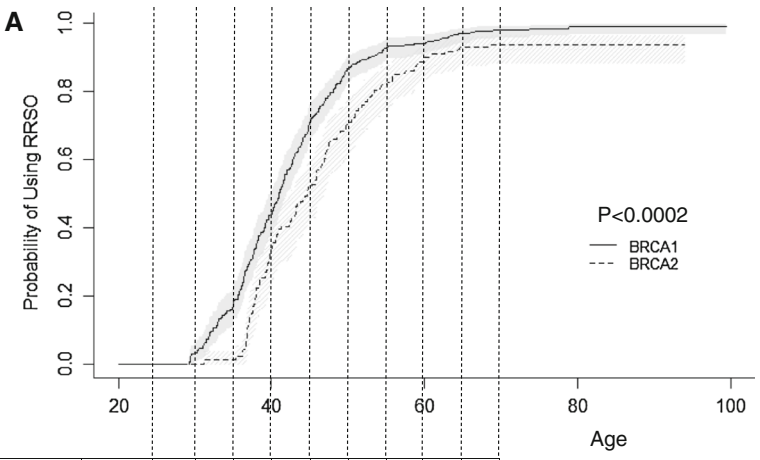
Results

We studied a prospective cohort of 1,499 women with disease-associated *BRCA1/2* mutations (Supplementary Table 1) born between 1899 and 1985 (Mean 1960). 927 (62 %) women had never undergone RRSO nor RRM, 444 (30 %; mean age at RRSO: 43.6 years) had undergone RRSO only, 171 (11 %; mean age at RRM: 37.4 years) had undergone RRM only, and 164 (11 %) underwent both RRSO and RRM. Other commonly occurring events included RRSO after a breast cancer diagnosis (139; 9 %), RRM after RRSO (74; 5 %), and RRSO before RRM (74; 5 %). Totals presented in Supplementary Table 1 and in this paragraph reflect the censoring of observations as described above. These figures reflect the number of observations actually used in analysis.

RRSO

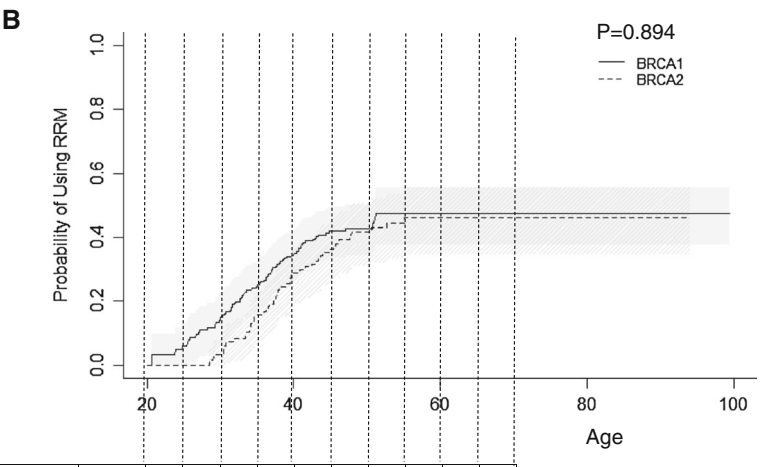
Age-specific utilization of RRSO is presented in Fig. 1a. *BRCA1* mutation carriers underwent RRSO more frequently than *BRCA2* mutation carriers ($P < 0.0002$). The cumulative probability estimates for RRSO indicate that most women with *BRCA1* or *BRCA2* mutation will undergo RRSO during their lifetime (98.5 vs. 93.4 % by age 70; Fig. 1a). RRSO occurred between age 29.3 and age 79 years in *BRCA1* mutation carriers (mean 43.0 years) and age 31.2 and age 68.5 in *BRCA2* mutation carriers (mean 46.3 years). RRSO was most commonly used by women aged 35–40. Overall, RRSO usage decreased after age 40. No RRSO was observed in *BRCA1* mutation carriers before age 25 and in *BRCA2* mutation carriers before age 30. The age-specific rate of RRSO usage was significantly higher in *BRCA1* compared with *BRCA2* mutation carriers ($P < 0.001$).

RRSO usage also differed by relative timing of mutation testing and by birth cohort. Before mutation testing, *BRCA1* mutation carriers were significantly more likely to undergo RRSO than *BRCA2* mutation carriers (Fig. 2a, $P = 0.025$), while there was no difference in the use of RRSO after mutation testing in *BRCA1* vs. *BRCA2* mutation carriers (Fig. 2b, $P = 0.415$). When stratified by birth cohort, *BRCA1* mutation carriers born in or before 1960 were significantly more likely to undergo RRSO than *BRCA2* mutation carriers (Fig. 2c, $P < 0.0002$). Among women born after 1960 or tested for mutation before age



	Age	25-30	30-35	35-40	40-45	45-50	50-55	55-60	60-65	65-70
Probability of RRSO Occurring in 5-Year Window	BRCA1	0.035	0.153	0.265	0.250	0.160	0.066	0.022	0.021	0.013
	BRCA2	0	0.025	0.293	0.202	0.185	0.116	0.068	0.036	0.009

Cumulative Probability of RRSO	BRCA1	0.035	0.188	0.453	0.703	0.863	0.929	0.951	0.972	0.985
	BRCA2	0	0.025	0.318	0.520	0.705	0.821	0.889	0.925	0.934



	Age	20-25	25-30	30-35	35-40	40-45	45-50	50-55	55-60	60-65	65-70
Probability of RRM Occurring in 5-Year Window	BRCA1	0.054	0.084	0.104	0.101	0.063	0.022	0.036	0	0	0
	BRCA2	0	0.042	0.105	0.133	0.085	0.059	0.031	0.010	0	0

Cumulative Probability of RRM	BRCA1	0.054	0.138	0.242	0.343	0.406	0.428	0.464	0.464	0.464	0.464
	BRCA2	0	0.042	0.147	0.280	0.365	0.424	0.455	0.465	0.465	0.465

Fig. 1 Kaplan–Meier estimates for the cumulative probability of surgery. **a** RRSO; **b** RRM

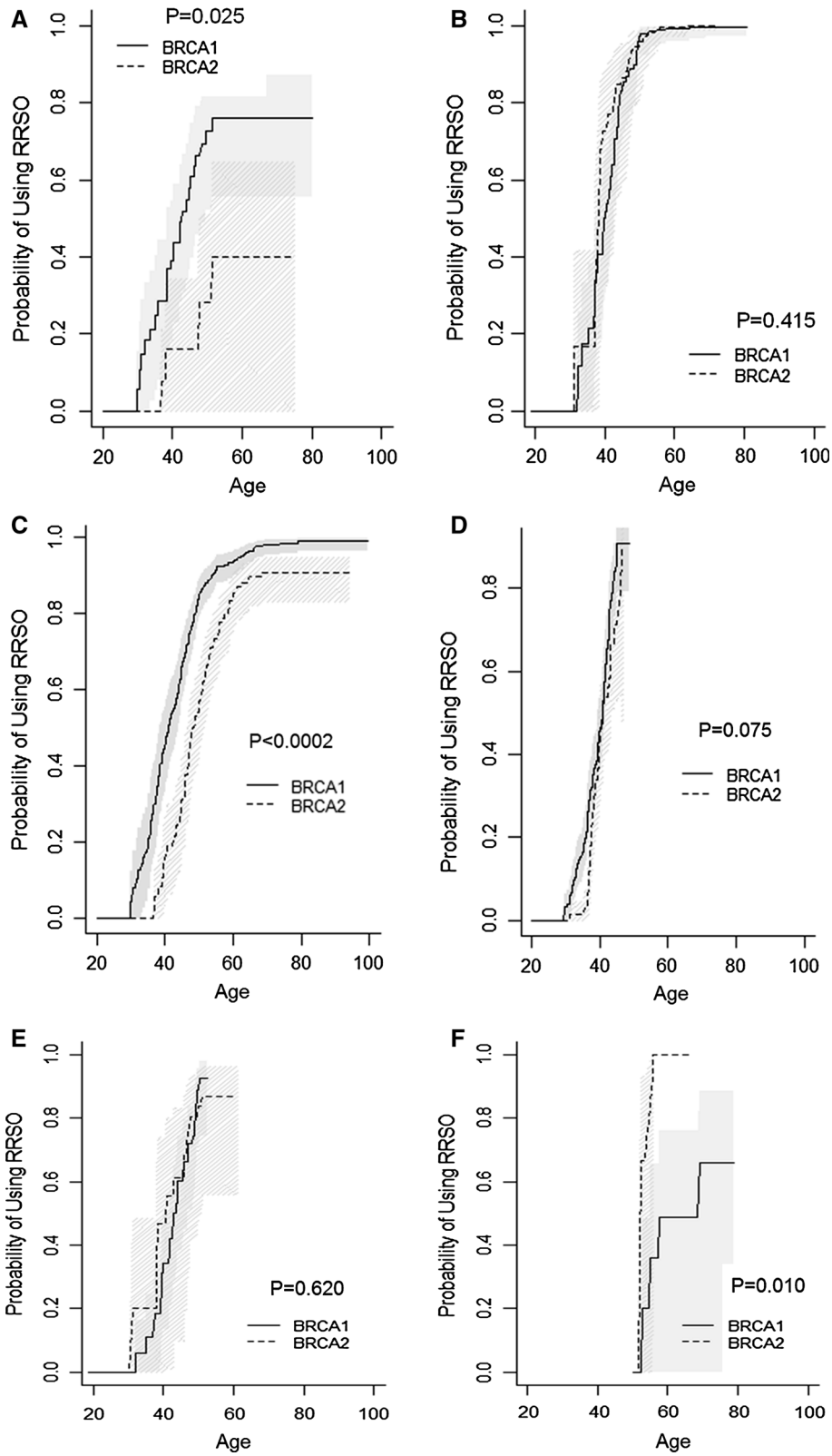


Fig. 2 Timing of RRSO relative to mutation testing. **a** RRSO before mutation testing; **b** RRSO after mutation testing; **c** Women born before or in 1960; **d** women born after 1960; **e** women tested before age 50 years (women excluded if follow-up was less than 0.5 years); **f** women tested after age 50 years (women excluded if follow-up was less than 0.5 years)

50 years, there was no difference in utilization of RRSO in *BRCA1* vs. *BRCA2* mutation carriers (Fig. 2d, $P = 0.075$; Fig. 2e, $P = 0.62$). Among women tested before age 50 years, the difference was significant (Fig. 2f, $P = 0.01$), but the P value needs to be interpreted with caution due to small sample size.

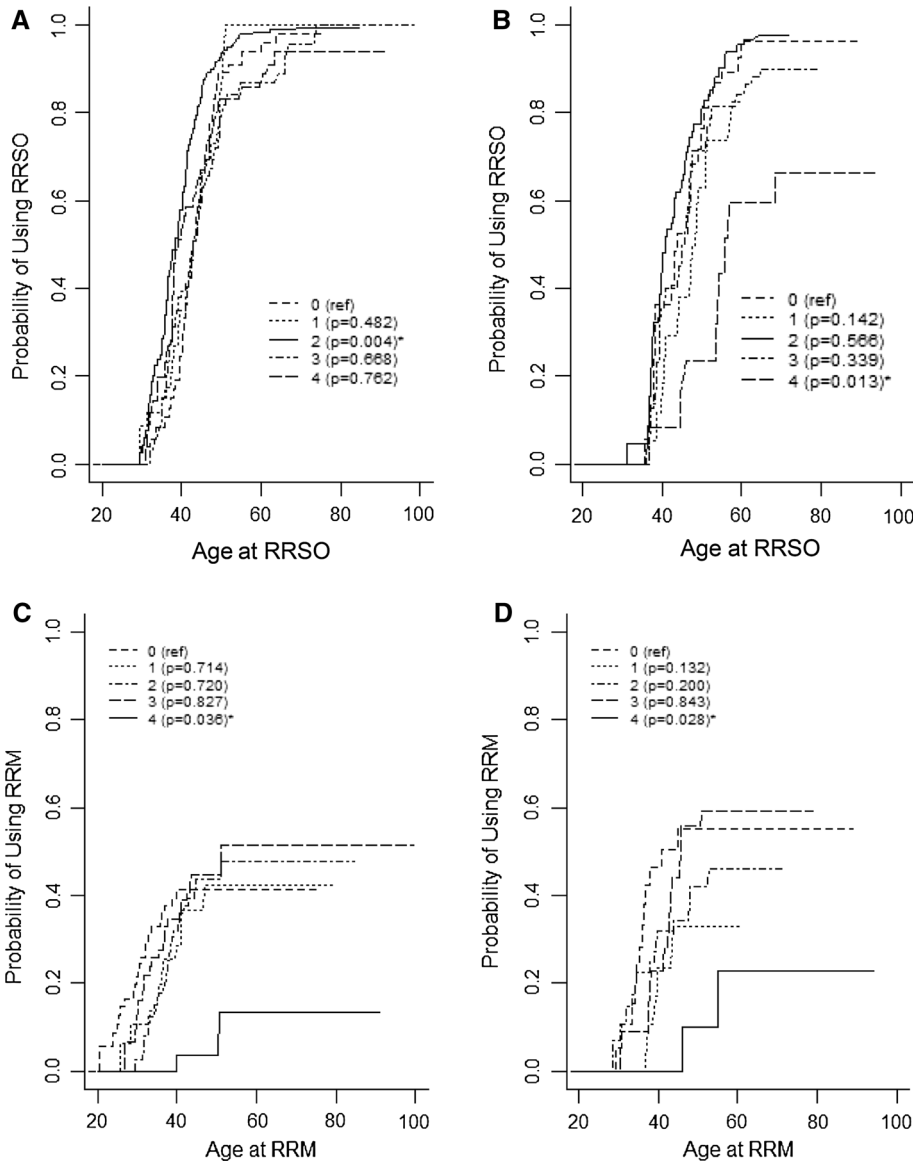


Fig. 3 Kaplan–Meier estimates for the cumulative probability of using surgery stratified by the number of live births. **a** RRSO-BRCA1; **b** RRSO-BRCA2; **c** RRM-BRCA1; **d** RRM-BRCA2

As most clinical recommendations regarding the use of RRSO refer to childbearing, family planning may also affect a woman's decision about the use of RRSO. Figure 3 presents Kaplan–Meier estimates for the probability of using RRSO stratified by number of live births. *BRCA1* mutation carriers who had two children were most likely to undergo RRSO (Fig. 3a, $P = 0.004$) compared with nulliparous women. *BRCA1* mutation carriers who had a history of 1, 3, or 4+ live births underwent RRSO similar to the nulliparous women. *BRCA2* mutation carriers who had four or more children were less likely to undergo RRSO (Fig. 3b, $P = 0.013$) compared with nulliparous women. *BRCA2* mutation carriers who had a history of 1–3 live births underwent RRSO similar to the nulliparous women. The estimated proportion of women who underwent RRSO by age is presented in Table 1.

The estimated proportion of women who underwent RRSO increased 1, 2, 5, and 10 years after being diagnosed with breast cancer (Table 2) to 66.2 % in *BRCA1* and 59.6 % in *BRCA2* 10 years after diagnosis. The increases were similar in those women who had been diagnosed with breast cancer before age 50 and among *BRCA2* mutation carriers diagnosed after 50, but the usage was lower among women who were diagnosed with breast cancer after age 50 in *BRCA1* mutation carriers (26.7 % 10 years after diagnosis).

RRM

Age-specific utilization of RRM is presented in Fig. 1b. *BRCA1* mutation carriers were estimated to undergo RRM as frequently as *BRCA2* mutation carriers by age 60, the age at the latest RRM (46 %; $P = 0.894$). The cumulative

Table 1 Estimated proportion of women using RRSO by age, birth cohort, and mutation testing

					Age (Mean and 95% CI)		
			Mean Age (Range)	Total Sample	35	45	50
		BRCA1	43.0 (29.3-79.0)	965	18.1 (12.5-23.4)	71.4 (65.6-76.2)	86.8 (82.5-90.0)
		BRCA2	46.3 (31.2-68.5)	534	1.3 (0-3.7)	51.9 (42.1-60.1)	70.9 (61.9-77.8)
Birth Cohort	Before/in 1960	BRCA1	45.9 (29.9-79.0)	460	21.0 (7.5-32.5)	66.4 (57.1-73.7)	84.7 (78.8-89.0)
		BRCA2	50.2 (36.7-68.5)	279	0	30.9 (17.5-42.0)	56.9 (44.2-66.7)
	After 1960	BRCA1	37.7 (29.3-45.1)	505	17.2 (10.8-23.1)	90.8 (79.1-95.9)	90.8 (79.1-95.9)
		BRCA2	39.2 (31.2-46.5)	255	1.5 (0-4.5)	71.1 (53.0-82.2)	89.1 (47.6-97.8)
Mutation Testing	Before	BRCA1	40.3 (29.9-51.5)	166	24.9 (5.3-40.4)	57.9 (36.8-72.0)	72.8 (52.2-84.5)
		BRCA2	43.4 (36.7-51.4)	95	0	16.1 (0-34.3)	28.1 (0-51.2)
	After	BRCA1	44.3 (32.1-69.3)	175	17.3 (0-33.3)	84.4 (70.7-91.7)	97.3 (91.1-99.2)
		BRCA2	47.8 (31.2-64.8)	118	16.7 (0-41.7)	86.4 (59.3-95.5)	96.0 (84.0-99.0)
Mutation Testing Age	Before 50	BRCA1	42.6 (32.1-50.3)	156	17.3 (0-33.3)	84.4 (70.7-91.7)	97.3 (91.1-99.2)
		BRCA2	42.9 (31.2-51.0)	91	16.7 (0-41.7)	86.4 (59.3-95.5)	96.0 (84.0-99.0)
	After 50	BRCA1	58.7 (52.6-69.3)	19	48.8 (0-76.0)*	79.5 (0-96.0)**	86.3 (15.3-97.8)***
		BRCA2	56.2 (50.9-64.8)	27	90.0 (25.5-98.7)*	100**	100***
Mutation Testing Age#	Before 50	BRCA1	43.3 (32.1-50.3)	112	5.9 (0-16.4)	60.2 (38.3-74.4)	88.8 (71.3-95.7)
		BRCA2	43.6 (31.2-51.0)	59	20.0 (0-48.4)	61.1 (9.7-83.2)	83.8 (48.9-94.9)
	After 50	BRCA1	58.6 (52.6-69.3)	15	36.0 (0-65.6)*	48.8 (0-76.0)**	65.9 (0-88.7)***
		BRCA2	55.9 (52.1-64.4)	14	77.8 (0-96.3)*	100**	100***
Live Births	Exactly 2	BRCA1	41.6 (29.4-69.3)	318	26.2(14.6-36.2)	84.4(76.3-89.7)	93.5(88.3-96.4)
	Not 2		44.1 (29.3-79.0)	625	13.6(7.4-19.4)	63.1(55.1-69.7)	82.3(75.7-87.1)
	Exactly 2	BRCA2	45.3 (31.2-64.4)	180	4.6(0-12.9)	64.7(48.9-75.5)	81.4(68.6-89.0)
	Not 2		47.2 (35.4-68.5)	345	0	43.2(30.1-53.9)	62.4(49.2-72.1)

* Rates are for age 55 years;

** Rates are for age 65 years;

*** Rates are for age 70 years;

Women who had less than 0.5 years of follow up were excluded.

Table 2 Estimated proportion of women (95 % CI) who underwent surgery 1, 2, 5, 10 years after being diagnosed with breast cancer or RRSO

	Years Since Breast Cancer:		1	2	5	10
RRSO Use After Breast Cancer	Overall	BRCA1	22.4 (15.7-28.5)	36.6 (28.4-43.8)	51.2 (41.5-59.4)	66.2 (53.2-75.6)
		BRCA2	17.4 (10.0-24.3)	27.3 (18.3-35.3)	41.6 (30.4-51.1)	59.6 (44.1-70.9)
	Breast cancer before age 50	BRCA1	23.5 (16.4-30.0)	38.6 (29.8-46.3)	53.5 (43.2-61.9)	69.0 (55.6-78.3)
		BRCA2	19.8 (10.6-28.1)	31.9 (20.7-41.5)	46.9 (33.5-57.6)	61.4 (43.5-73.6)
	Breast cancer after age 50	BRCA1	12.6 (0-27.6)	26.7 (0.2-46.1)	26.7 (0.2-46.1)	26.7 (0.2-46.1)
		BRCA2	10.7 (0-21.5)	14.4 (0.3-26.6)	25.8 (4.7-42.3)	57.6 (15.6-78.7)
	Years Since RRSO:		1	2	5	10
RRM Use After RRSO		BRCA1	8.6 (5.2-11.9)	13.8 (9.5-18.0)	19.1 (13.7-24.1)	29.1 (20.1-37.1)
		BRCA2	9.7 (4.0-14.9)	11.6 (5.5-17.4)	17.9 (9.8-25.3)	20.3 (11.0-28.6)

probability estimates for RRM indicate that about half of women with either *BRCA1* or *BRCA2* mutation will undergo RRM during their lifetime (Fig. 1b). The earliest RRM occurred at age 20.6 in *BRCA1* mutation carriers and age 28.6 in *BRCA2* mutation carriers. RRM was most commonly used by women aged 30–35 in *BRCA1* mutation carriers and in ages 35–40 in *BRCA2* mutation carriers. RRM usage decreased after age 40, with no RRM after age 55 in *BRCA1* and none after age 60 in *BRCA2* mutation carriers. RRM usage did not differ significantly by birth cohort, and data was insufficient to compare RRM usage by relative timing of mutation testing (Fig. 4).

Unlike oophorectomy, which is influenced by reproductive choices, there is no recommendation for RRM relative to childbearing. Figure 3c, d presents Kaplan–Meier estimates for the probability of using RRM stratified by number of live births. *BRCA1* and *BRCA2* mutation carriers who had four or more children were least likely to undergo RRM ($P = 0.036$ and $P = 0.028$, respectively) compared with nulliparous women. *BRCA1* mutation carriers who had a history of 1, 2, or 3 live births used RRM similarly to nulliparous women. This likely reflects delay of RRM among women who choose to have more children.

RRM and RRSO

164 women underwent both RRSO and RRM. Of these, 74 underwent RRM before RRSO, 43 occurred simultaneously,

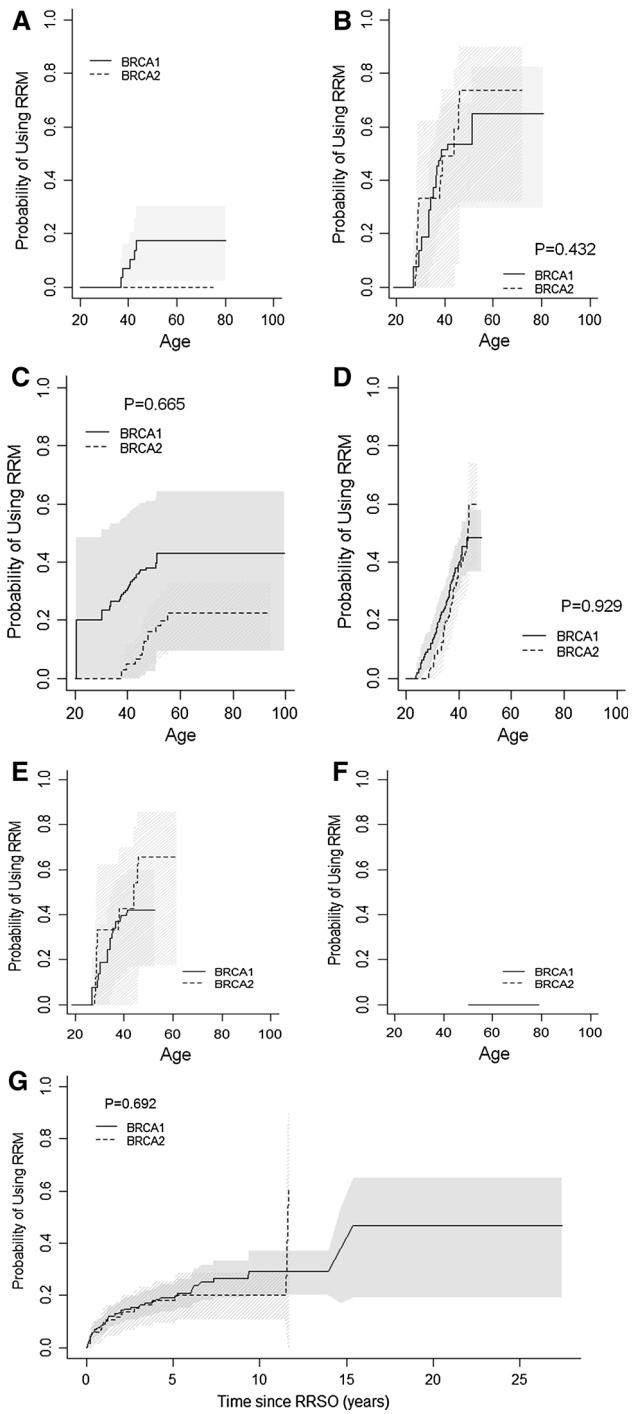


Fig. 4 Kaplan–Meier estimates for the cumulative probability of RRM. **a** Before mutation testing (No *P* value could be computed as no BRCA2 carriers underwent RRM before mutation testing); **b** after mutation testing; **c** women born before or during 1960; **d** women born after 1960; **e** women tested before age 50 years (women excluded if follow-up was less than 0.5 years); **f** women tested after age 50 years (women excluded if follow-up was less than 0.5 years); **g** women who had previously undergone RRSO

and 74 underwent RRM after RRSO. None of the *BRCA2* women whose mutation test happened after age 50 years underwent RRM, while there was only one *BRCA1* woman whose mutation test happened after age 50 years underwent RRM.

The correlation between age of RRM and age of RRSO was 0.90 ($P < 0.0001$). We observed no difference in the cumulative probability of RRM after RRSO by *BRCA1/2* status ($P = 0.692$). The estimated proportion of women who underwent RRM increased 1, 2, 5, and 10 years after RRSO (Table 2; Supplementary Fig. 1) to 29.1 % in *BRCA1* and 20.3 % in *BRCA2* 10 years after diagnosis.

Discussion

We used a prospective cohort of *BRCA1/2* mutation-positive women to evaluate usage of RRSO and RRM. We modeled the lifetime utilization of RRSO and RRM and showed that uptake of RRSO is improved in *BRCA2* carriers after genetic testing. We also identified childbearing as having an influence on utilization of both RRSO and RRM. Finally, we estimated the usage of RRSO and RRM after a breast cancer diagnosis and the use of RRM after RRSO. Our results showed that uptake of RRSO is high, but usage occurs later than recommended. *BRCA2* mutation carriers do not undergo RRSO as often as *BRCA1* mutation carriers until they have been genetically tested.

The present results represent an advance over prior studies of this type because we have used failure-time analyses in a prospective cohort to estimate usage of RRSO and RRM. Most previous studies have used retrospective cohorts, case-series, or cross-sectional studies to describe the usage of RRSO and/or RRM without accounting for follow-up or other events (e.g., other preventive surgeries or cancer diagnoses) [2, 4, 9, 10, 12, 14, 21, 22]. These previous studies have estimated wide ranges of RRSO or RRM usage from less than 30 % to over 75 % depending on the study sample or ascertainment strategy. Most concluded that RRSO is underutilized. Similar variability in the timing of surgery with respect to age or reproductive history has been reported.

Here, we demonstrate that RRSO is estimated to be used by most women in their lifetime, as would be recommended by most professional bodies. It has been suggested that RRSO does not always occur during the period these organizations would recommend, usually by age 40 or after completion of childbearing. Our data suggest that about

86 % of *BRCA1* mutation carriers and 71 % of *BRCA2* mutation carriers undergo RRSO by age 50. In previous series, ovarian cancer is diagnosed in a non-trivial proportion of women with *BRCA1/2* mutations before age 50. The earliest documented ovarian cancer in the PROSE data set was diagnosed at age 30.1 years, but it is rare for ovarian cancer to be diagnosed before age 40. In *BRCA1* mutation carriers from the PROSE data, we observed 29 ovarian cancer cases before the age of 50 (3 %), including 7 before the age of 40 (0.7 %), and 2 before the age of 35 (0.2 %) among 965 *BRCA1* mutation carriers. In *BRCA2* mutation carriers from the PROSE data, we observed 3 ovarian cancer cases before the age of 50 (0.06 %), none before the age of 40, and none before the age of 35 among 534 *BRCA2* mutation carriers. These values are similar to those reported previously in large retrospective cohorts [19]. Given the early age of some ovarian cancers, and the current inability to identify which women will develop these early cancers, underutilization of RRSO is a major concern.

Because other prevention and early detection strategies are available for breast cancer, including mammography and MRI screening, use of selective estrogen receptor modifiers, and other interventions, RRM is an option rather than a mandate. In the present data, we estimate that less than half of *BRCA1/2* mutation carriers undergo RRM in their lifetime, with most surgeries occurring between the ages of 25–45.

While there are substantial benefits to RRSO and RRM, these surgical interventions are not without potentially negative psychosocial or medical consequences, and RRSO/RRM should be only undertaken in the context of genetic counseling that lays out the risks and benefits to ensure optimal decision-making by each patient. The body of literature regarding factors that influence decision-making suggests that decisions about RRSO and RRM are determined by psychosocial factors, mutation carriage, age, and prior cancer [22–28].

The present study has many advantages over prior studies, but it remains limited in a number of ways. First, we only consider the use of RRSO and RRM. Other preventive practices including secondary breast and ovarian screening occurred during the follow-up period. As an observational study, as opposed to a randomized trial, we were not able to account completely for the use of other preventive strategies as has been done in other studies [16, 17]. These may have influenced some women's use of RRSO or RRM. Second, while our prospectively ascertained sample is large, we have relatively small observations in some subgroups. Indeed, as shown in Table 1, some events were represented by only a handful of participants. It was therefore difficult to obtain statistically significant inferences about some groups of interest. Finally, the sample set studied here came from referral centers, which may not represent the entire population receiving genetic testing for *BRCA1/2*. However, these centers are representative of settings in which genetic testing and counseling practices would be performed today.

Our results support the knowledge that genetic testing and counseling increase the usage of RRSO in *BRCA2* mutation carriers. Lifetime use of RRSO is estimated to be very high, but the timing of these surgeries remains suboptimal for cancer prevention in *BRCA1/2* mutation carriers.

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Conflict of interest None.

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