Association between risk-reducing surgeries and survival in young *BRCA* carriers with breast cancer: an international cohort study

Eva Blondeaux, Amir Sonnenblick*, Elisa Agostinetto, Raphaëlle Bas, Hee J Kim, Maria A Franzoi, Rinat Bernstein-Molho, Sabine Linn, Ava Kwong, Katarzyna Pogoda, Judith Balmana, Ann Smeets, Jyoti Bajpai, Halle C F Moore, Ann H Partridge, Kelly-Anne Phillips, Angela Toss, Christine Rousset-Jablonski, Fedro A Peccatori, Tiphaine Renaud, Alberta Ferrari, Shani Paluch-Shimon, Pablo Mando, Jeong E Lee, Robert Fruscio, Wanda Cui, Stephanie M Wong, Claudio Vernieri, Kathryn J Ruddy, Maria V Dieci, Alexios Matikas, Mariya Rozenblit, Deniz C Guven, Minna Lee, Cynthia Villarreal-Garza, Shelley E Hwang, Laura De Marchis, Fabio Puglisi, Zoe Kemp, Pedro A Meireles, Anastasia Parokonnaya, Gustavo Werutsky, Maiko Okano, Hatem A Azim Jr, Kleida Mati, Shoshana Rosenberg, Richard Gelber, Luca Boni, Matteo Lambertini*

Summary

Background Little evidence exists on the effect of risk-reducing surgeries in young *BRCA* carriers with a previous history of breast cancer. We investigated the association between risk-reducing mastectomy (RRM) or risk-reducing salpingo-oophorectomy (RRSO), or both procedures, with survival outcomes in a large global cohort of young *BRCA* carriers with previous breast cancer.

Methods The BRCA BCY Collaboration is an international, hospital-based, retrospective cohort study, conducted at 109 centres in five continents, including women harbouring germline *BRCA1*, *BRCA2*, or both, pathogenic or likely pathogenic variants and diagnosed with stage I–III invasive breast cancer at the age of 40 years or younger between Jan 1, 2000, and Dec 31, 2020. The primary objectives of the present analysis were to determine the association between RRM or RRSO and overall survival in young *BRCA* carriers with breast cancer. The primary endpoint was overall survival. This study is registered with ClinicalTrials.gov, NCT03673306.

Findings Between Jan 1, 2000 and Dec 31, 2020, 5290 patients were included, of whom 3361 (63·5%) patients were *BRCA1* pathogenic variant carriers, 2708 (51·2%) had node-negative, and 2421 (45·8%) hormone receptor-positive breast cancer. Of 5290 patients, 2910 (55·0%) underwent RRM, 2782 (52·6%) underwent RRSO. After a median follow-up of 8·2 years (IQR 4·7–12·8), RRM was associated with significantly better overall survival compared with no RRM (adjusted HR [aHR] 0·65, 95% CI 0·53–0·78; 20-year restricted mean overall survival time 17·89 years [95% CI 17·61–18·17] with RRM *vs* 16·65 years [16·38–16·92] without RRM). RRSO was also associated with significantly better overall survival compared with no RRSO (aHR 0·58, 95% CI 0·48–0·71; 20-year restricted mean overall survival time 17·73 years [95% CI 17·43–18·03] with RRSO *vs* 16·67 years [16·38–16·96] without RRSO).

Interpretation In this global cohort of *BRCA* carriers with previous breast cancer diagnosis at a young age, RRM and RRSO were both associated with a significant improvement in overall survival. These findings provide evidence for a tailored counselling of a unique and high-risk patient population on cancer risk management strategies.

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*Contributed equally

Clinical Trial Unit, Epidemiologia Clinica, Ospedale Policlinico San Martino, Genova, Italy (E Blondeaux MD, L Boni MD); **The Oncology Division, Tel Aviv Sourasky Medical Center, Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel** (A Sonnenblick MD); **Université libre de Bruxelles, Hôpital Universitaire de Bruxelles, Institut Jules Bordet, Service de Oncologie, Brussels, Belgium** (E Agostinetto MD); **Department of Medical Oncology, Universite Paris Cité, Institut Curie, Paris, France** (R Bas MD); **Division of Breast Surgery, Department of Surgery, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea** (Prof H J Kim MD); **Cancer Survivorship Group, Gustave Roussy, Villejuif, France** (M A Franzoi MD); **INSERM U981, Villejuif, France** (M A Franzoi); **Susanne Levy Gertner Oncogenetics Unit, The Danek Gertner Institute of Human Genetics, Chaim Sheba Medical Center affiliated to Tel Aviv University, Tel Hashomer, Israel** (R Bernstein-Molho MD); **Department of Medical Oncology, Netherlands Cancer Institute, Amsterdam, Netherlands** (S Linn MD); **Department of Pathology, University Medical Center Utrecht, Utrecht, Netherlands** (S Linn); **Hong Kong Hereditary**

Introduction

Women with germline pathogenic or likely pathogenic variants in *BRCA1* or *BRCA2* genes face a lifetime risk for breast cancer of approximately 40–70% and a risk for ovarian cancer of 10–50%, depending on the affected *BRCA* gene.[1,2] Cancer risk management strategies are widely recommended in *BRCA* healthy carriers,[3] due to their impact on reducing cancer risk.[4–7]

Counselling *BRCA* carriers with history of breast cancer regarding bilateral risk-reducing mastectomy (RRM) and risk-reducing salpingo-oophorectomy (RRSO) is particularly challenging, especially among women with a first breast cancer diagnosis at a young age considering the scarce available evidence. Indeed, risk of relapse of their primary breast cancer should be balanced with the risk of developing a second primary malignancy.[8–10] In this setting, RRM reduces the risk of contralateral breast cancer,[11–13] and RRSO reduces both the risk of ovarian cancer and breast cancer through the reduction of circulating oestrogen.[6,7,14] Some studies indicated that among *BRCA* carriers of all ages with previous history of breast cancer, RRSO might also lead to a survival advantage.[15,16] However, no study has focused specifically on the role of risk-reducing surgeries among *BRCA* carriers with previous breast cancer diagnosis at a young age. Considering the unique features and needs of this

Breast Cancer Family Registry, Hong Kong (Prof A Kwong PhD); **Cancer Genetics Centre and Breast Surgery Centre, Hong Kong Sanatorium and Hospital, Hong Kong** (Prof A Kwong); **Department of Surgery, The University of Hong Kong, Hong Kong** (Prof A Kwong); **Department of Breast Cancer and Reconstructive Surgery, Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland** (K Pogoda MD); **Hereditary Cancer Genetics Unit, Medical Oncology Department, Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology, Barcelona, Spain** (J Balmana MD); **Department of Surgical Oncology, University Hospitals Leuven, KU Leuven, Leuven, Belgium** (A Smeets MD); **Tata Memorial Centre, Homi Bhabha National Institute, Mumbai, India** (J Bajpai MD); **Cleveland Clinic Lerner College of Medicine at Case Western Reserve University, Cleveland, OH, USA** (Prof H C F Moore MD); **Department of Hematology and Medical Oncology, Cleveland Clinic, Cleveland, OH, USA** (Prof H C F Moore); **Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, USA** (A H Partridge MD); **Department of Medical Oncology, Peter MacCallum Cancer Centre, Melbourne, VIC, Australia** (Prof K-A Phillips MD, W Cui MBBS); **Sir Peter MacCallum Department of Oncology, The University of Melbourne, Melbourne, VIC, Australia** (K-A Phillips, W Cui); **Department of Oncology and Haematology, Azienda Ospedaliero-Universitaria Policlinico di Modena, Modena, Italy** (A Toss MD); **Department of Medical and Surgical Sciences, University of Modena and Reggio Emilia, Modena, Italy** (A Toss); **Department of Surgery, Leon Berard Cancer Center, Lyon, France** (C Rousset-Jablonski MD); **INSERM 1290 RESHAPE, Lyon, France** (C Rousset-Jablonski MD); **Hôpital Femme Mère Enfant, Bron, France** (C Rousset-Jablonski); **Gynecologic Oncology Department, European Institute of Oncology, Milan, Italy** (F A Peccatori, PhD); **Cancer Genetics Unit, Bergonie**

Research in context

Evidence before this study

Women with germline pathogenic or likely pathogenic variants in *BRCA1, BRCA2*, or both, genes face substantially elevated lifetime risks of breast and ovarian cancers. Cancer risk management strategies including bilateral risk-reducing mastectomy (RRM) and risk-reducing salpingo-oophorectomy (RRSO) are widely recommended in *BRCA* carriers who are otherwise healthy. However, in *BRCA* carriers with a previous history of breast cancer, additional challenges should be considered in the counselling regarding risk-reducing surgeries, especially among young patients. The risk of relapse of their primary breast cancer should be balanced with the risk of developing a second primary malignancy. Moreover, although both surgical procedures are known to reduce cancer risk, only RRSO has consistently been shown to improve overall survival in *BRCA* carriers of all ages with previous history of breast cancer, whereas the effect of RRM in reducing mortality remains controversial. In young women specifically, these surgical interventions have an impact on reproductive plans and quality of life. In order to identify the available evidence in this field before we conducted the present study and to contextualise its results, we searched PubMed from database inception to identify previously published articles on risk-reducing surgeries in *BRCA* carriers with previous history of breast cancer without language or date restrictions on Nov 30, 2024, using the search terms "*BRCA*" AND "breast cancer" AND "(risk-reducing surgeries OR risk-reducing mastectomy OR risk-reducing salpingo-oophorectomy)". The retrieved records were reviewed to assess the existing available literature on this topic. The identified studies have often combined older and younger *BRCA* carriers or healthy carriers, leaving a gap in evidence specifically for young *BRCA* carriers with a previous history of breast cancer. Therefore, before conducting the present analysis, we could not identify any previous study focused specifically on the role of RRM or RRSO among *BRCA* carriers with previous history of breast cancer at a young age (defined as aged 40 years or younger at diagnosis).

Added value of this study

To our knowledge, this global, multicentre, retrospective cohort study provides the largest analysis to date of young *BRCA* carriers with previous early-onset breast cancer (≤40 years old at diagnosis), investigating the association between RRM or RRSO and survival outcomes. Results indicate that both RRM and RRSO were independently associated with improved overall survival. These findings provide evidence about the role of risk-reducing surgeries in this unique and high-risk patient population.

Implications of all the available evidence

This study underscores the importance of *BRCA* testing and personalised counselling regarding risk-reducing surgeries for *BRCA* carriers with young-onset breast cancer. Based on this evidence, RRM and RRSO were associated with a significant improvement in survival outcomes, justifying their consideration in tailored cancer risk management strategies for this special population. Future research should focus on long-term follow-up and patient-centred outcomes, including quality of life and reproductive considerations, to optimise shared decision-making processes.

patient population, as well as the impact of such interventions on their reproductive plans and quality of life,[17] it is essential to provide evidence in this regard to individualise counselling.

This study investigated the association between RRM or RRSO and survival outcomes in a large global cohort of young *BRCA* carriers with previous history of breast cancer.

Methods

Study design and participants

The BRCA BCY Collaboration is an international, multicentre, hospital-based, retrospective cohort study including young *BRCA* carriers with breast cancer.[18]

To be eligible for inclusion, female participants (sex was assigned based on medical records) had to be diagnosed with invasive breast cancer at age 40 years or younger between Jan 1, 2000, and Dec 31, 2020, and to carry germline pathogenic or likely pathogenic variants in the *BRCA1, BRCA2,* or both, genes. Healthy *BRCA* carriers or patients with *BRCA* variants of unknown significance, non-invasive breast cancer, or history of other malignancies without breast cancer diagnosis as well as patients with de-novo stage IV breast cancer, no information on uptake or timing of RRM or RRSO, or their uptake before breast cancer diagnosis were excluded.

The Institut Jules Bordet (Brussels, Belgium) acted as the coordinating centre and the central ethics committee. The study received ethical approval from the local, regional, or national institutional review boards of participating centres, whenever required by regulations.

This study is registered with ClinicalTrials.gov, NCT03673306.

Procedures

Data collected from medical records or questionnaires for all eligible patients included breast cancer history and treatment, type of germline *BRCA* pathogenic or likely pathogenic variants, recurrence data, survival, and risk-reducing surgeries. *BRCA* testing, diagnostic and staging workup, treatment, and follow-up were performed by each centre according to clinical practice. Information on ethnicity or race was not collected.

For primary breast cancer treatment, patients could have undergone either breast-conserving surgery or mastectomy as the primary surgery. RRM was defined as the uptake of bilateral (in case of prior conservative breast surgery) or contralateral (in case of mastectomy for the affected side)

mastectomy. RRSO was defined as the uptake of bilateral salpingo-oophorectomy.

This work adheres to the STROBE statement guidelines.[19]

Outcomes

The primary endpoint was overall survival defined as the length of time from breast cancer diagnosis to death from any cause.[20] Secondary endpoints were disease-free survival (defined as the length of time from breast cancer diagnosis to the development of any of the following events: locoregional or distant recurrence, second primary breast cancer, second primary malignancy, or death from any cause),[20] breast cancer-free interval (defined as time from breast cancer diagnosis to the development of any of the following events: locoregional recurrence, distant recurrence, second primary breast cancer, or death from breast cancer cause),[20] incidence of second primary breast cancer, and incidence of ovarian or fallopian tube cancer.

Statistical analysis

The primary objectives of the present analysis were to determine the association between RRM or RRSO and overall survival in young *BRCA* carriers with breast cancer. Secondary objectives were to determine the association between RRM or RRSO and disease-free survival or breast cancer-free interval or incidence of second breast cancer or incidence of ovarian or fallopian tube cancer, to describe patients' tumour and treatment characteristics at diagnosis according to uptake of RRM and RRSO, and to determine the association between RRM and RRSO and overall survival in different prespecified subgroups of patients according to: age at the time of breast cancer diagnosis (aged ≤30 years *vs* 31–35 years *vs* 36–40 years), specific *BRCA* gene (*BRCA1 vs BRCA2*), tumour subtype (luminal-like *vs* triple negative *vs* HER2-positive), primary tumour size (T1 *vs* T2 *vs* T3–4), primary nodal status (N0 *vs* N1 *vs* N2–3), chemotherapy treatment (yes *vs* no), timing of *BRCA* testing (test before or at diagnosis *vs* test after diagnosis) and income (low–middle income *vs* high income). The immuno-histochemistry definition was used for classifying tumour subtypes.[21] Patients who received *BRCA* testing any time before breast cancer diagnosis and to up to 6 months after breast cancer diagnosis were considered as tested before or at diagnosis, whereas patients that received *BRCA* testing more than 6 months since breast cancer diagnosis were considered as tested after diagnosis.[22] Income was defined according to the World Bank 2024 income groups.

Descriptive statistics were used to summarise continuous and categorical variables. Continuous variables were reported as median (IQR), whereas categorical variables as frequencies and percentages.

Median follow-up from breast cancer diagnosis in the entire cohort was computed with the reverse Kaplan–Meier method.[23] Median follow-up after risk reducing surgeries was computed similarly by including only patients who underwent RRM or RRSO.

In order to explore the association between risk-reducing surgeries and survival outcomes, Cox models were used with RRM and RRSO included as time-dependent covariates. Patients who underwent RRM or RRSO at the time of breast cancer diagnosis were considered in the RRM or RRSO group from the beginning of the observation period. Both unadjusted and adjusted models were carried out. Adjusted models included as stratification factors variables that were associated with overall survival with a p value <0·20 in univariate analysis in the entire patient cohort (ie, year at breast cancer diagnosis, region, and nodal status). Since the decision to undergo RRM or RRSO could be influenced by the development of distant recurrences or second primaries, the multivariable models for overall survival were also adjusted by development of distant recurrences or second primaries as time-dependent covariates. Since the Kaplan–Meier method does not account for time-dependent covariates, we employed the Simon and Makuch method, which considers changes in an individual's covariate status over time, to plot survival curves.[24,25] The 20-year restricted mean survival time for each group were reported.

Institute, Bordeaux, France (T Renaud MD); **Hereditary Breast and Ovarian Cancer Unit and General Surgery 3—Senology, Breast Cancer Center, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy** (A Ferrari MD); **University of Pavia, Pavia, Italy** (A Ferrari); **Sharett Institute of Oncology, Hadassah University Hospital and Faculty of Medicine, Hebrew University, Jerusalem, Israel** (S Paluch-Shimon MD); **SUMA Argentina** (P Mando MD); **Sungkyunkwan University School of Medicine, Samsung Medical Center, Seoul, South Korea** (J E Lee MD); **UO Gynecology, IRCCS San Gerardo dei Tintori, Monza, Italy** (R Fruscio MD); **Department of Medicine and Surgery, University of Milan-Bicocca, Milan, Italy** (R Fruscio); **Department of Surgery and Oncology, Jewish General**

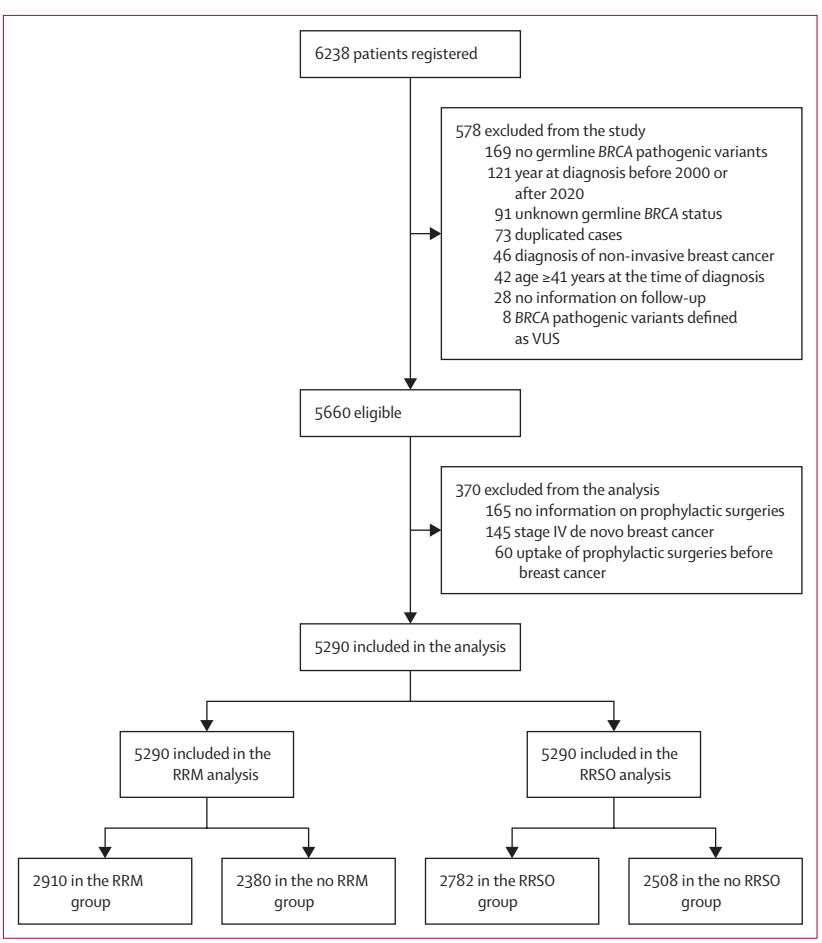

Figure 1: **Study profile**
RRM=risk-reducing mastectomy. RRSO=risk-reducing salpingo-oophorectomy. VUS=variant of unknown significance.

Hospital Segal Cancer Centre, Montreal, QC, Canada (S M Wong MD); **Medical Oncology Department, Breast Unit, Fondazione IRCCS Istituto Nazionale dei Tumori, Milano, Italy** (C Vernieri MD); **Oncology and Hematology-Oncology Department, University of Milan, Milan, Italy** (C Vernieri); **Department of Oncology, Mayo Clinic, Rochester, MN, USA** (K J Ruddy MD); **Dipartimento di Scienze Chirurgiche, Oncologiche e Gastroenterologiche, Università di Padova, Padova, Italy** (M V Dieci MD); **Oncologia 2, Istituto Oncologico Veneto IRCCS, Padova, Italy** (M V Dieci); **Department of Oncology–Pathology, Karolinska Institute and Breast Center, Karolinska University Hospital, Stockholm, Sweden** (A Matikas MD); **Yale University, Medical Oncology, Yale New Haven, CT, USA** (M Rozenblit MD); **Hacettepe University Cancer Institute, Ankara, Turkey** (D C Guven MD); **Breast Service, Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, NY, USA** (M Lee MD); **Breast Cancer Center, Hospital Zambrano Hellion –TecSalud, Tecnologico de Monterrey, Monterrey, Mexico** (C Villarreal-Garza MD); **Department of Surgery, Duke University, Durham, NC, USA** (S E Hwang MD); **Division of Medical Oncology, Department of Radiological, Oncological and Pathological Sciences, Sapienza University of Rome, Rome, Italy** (L De Marchis MD); **Medical Oncology Unit Department of Hematology, Oncology, Dermatology Umberto I University Hospital, Rome, Italy** (L De Marchis); **Department of Medical Oncology, Centro di Riferimento Oncologico di Avano–CRO IRCCS, Aviano, Italy** (F Puglisi MD); **Department of Medicine, University of Udine, Udine, Italy** (F Puglisi); **Breast Medical Oncology and Cancer Genetics Units, Royal Marsden Hospital, London, UK** (Z Kemp MD); **Medical Oncology Department, Instituto Português de Oncologia de Lisboa Francisco Gentil, Lisbon, Portugal** (P A Meireles MD); **National Medical Research Center of Oncology named after N N Blokhin of the**

	Overall cohort (n=5290)	No RRM group (n=2380)	RRM group (n=2910)	No RRSO group (n=2508)	RRSO group (n=2782)
Patient characteristics					
Region					
Latin America and South America	271 (5·1%)	129 (5·4%)	142 (4·9%)	158 (6·3%)	113 (4·1%)
Australia and Oceania	179 (3·4%)	62 (2·6%)	117 (4·0%)	75 (3·0%)	104 (3·7%)
Northern Europe	741 (14·0%)	260 (10·9%)	481 (16·5%)	303 (12·1%)	438 (15·7%)
Eastern Europe	316 (6·0%)	164 (6·9%)	152 (5·2%)	162 (6·5%)	154 (5·5%)
North America	629 (11·9%)	149 (6·3%)	480 (16·5%)	217 (8·7%)	412 (14·8%)
Southern Europe	2059 (38·9%)	847 (35·6%)	1212 (41·6%)	993 (39·6%)	1066 (38·3%)
Asia	1088 (20·6%)	763 (32·1%)	325 (11·2%)	593 (23·6%)	495 (17·8%)
Africa	7 (0·1%)	6 (0·3%)	1 (0·0%)	7 (0·3%)	0
Income					
Low–middle	706 (13·3%)	473 (19·9%)	233 (8·0%)	445 (17·7%)	261 (9·4%)
High	4584 (86·7%)	1907 (80·1%)	2677 (92·0%)	2063 (82·3%)	2521 (90·6%)
Year of diagnosis					
2000–04	653 (12·3%)	366 (15·4%)	287 (9·9%)	212 (8·5%)	441 (15·9%)
2005–08	843 (15·9%)	429 (18·0%)	414 (14·2%)	297 (11·8%)	546 (19·6%)
2009–12	1119 (21·2%)	529 (22·2%)	590 (20·3%)	490 (19·5%)	629 (22·6%)
2013–16	1330 (25·1%)	560 (23·5%)	770 (26·5%)	678 (27·0%)	652 (23·4%)
2017–20	1345 (25·4%)	496 (20·8%)	849 (29·2%)	831 (33·1%)	514 (18·5%)
Median age at diagnosis, years	35·0 (31·0–38·0)	35·0 (31·0–38·0)	35·0 (31·0–38·0)	33·0 (30·0–36·0)	36·0 (33·0–38·0)
Age at diagnosis, years					
≤30	1105 (20·9%)	482 (20·3%)	623 (21·4%)	770 (30·7%)	335 (12·0%)
31–35	1929 (36·5%)	876 (36·8%)	1053 (36·2%)	1019 (40·6%)	910 (32·7%)
36–40	2256 (42·6%)	1022 (42·9%)	1234 (42·4%)	719 (28·7%)	1537 (55·2%)
Median number of pregnancies before diagnosis	1·0 (0·0–2·0)	1·0 (0·0–2·0)	1·0 (0·0–2·0)	1·0 (0·0–2·0)	2·0 (1·0–3·0)
Specific *BRCA* gene					
BRCA1	3361 (63·5%)	1463 (61·5%)	1898 (65·2%)	1593 (63·5%)	1768 (63·6%)
BRCA2	1891 (35·7%)	896 (37·6%)	995 (34·2%)	892 (35·6%)	999 (35·9%)
BRCA1 and *BRCA2*	31 (0·6%)	16 (0·7%)	15 (0·5%)	16 (0·6%)	15 (0·5%)
BRCA-mutated (unknown if *BRCA1* or *BRCA2*)	7 (0·1%)	5 (0·2%)	2 (0·1%)	7 (0·3%)	0
Median time to *BRCA* test, years	0·5 (0·1–2·3)	1·1 (0·2–4·4)	0·3 (0·0–1·0)	0·4 (0·1–2·1)	0·5 (0·1–2·5)
Timing of *BRCA* testing					
Tested before or at diagnosis	2581 (48·8%)	863 (36·3%)	1718 (59·0%)	1255 (50·0%)	1326 (47·7%)
Tested after diagnosis	2411 (45·6%)	1400 (58·8%)	1011 (34·7%)	1101 (43·9%)	1310 (47·1%)
Unknown date of *BRCA* testing	298 (5·6%)	117 (4·9%)	181 (6·2%)	152 (6·1%)	146 (5·2%)
Tumour characteristics					
Tumour histology					
Ductal	4410 (83·4%)	2000 (84·0%)	2410 (82·8%)	2110 (84·1%)	2300 (82·7%)
Other	722 (13·6%)	344 (14·5%)	378 (13·0%)	351 (14·0%)	371 (13·3%)
Unknown	158 (3·0%)	36 (1·5%)	122 (4·2%)	47 (1·9%)	111 (4·0%)
Tumour size					
T1	1929 (36·5%)	777 (32·6%)	1152 (39·6%)	841 (33·5%)	1088 (39·1%)
T2	2411 (45·6%)	1106 (46·5%)	1305 (44·8%)	1158 (46·2%)	1253 (45·0%)
T3–4	719 (13·6%)	358 (15·0%)	361 (12·4%)	392 (15·6%)	327 (11·8%)
Unknown	231 (4·4%)	139 (5·8%)	92 (3·2%)	117 (4·7%)	114 (4·1%)
Nodal status					
N0	2708 (51·2%)	1133 (47·6%)	1575 (54·1%)	1262 (50·3%)	1446 (52·0%)
N1	1758 (33·2%)	788 (33·1%)	970 (33·3%)	822 (32·8%)	936 (33·6%)
N2–3	643 (12·2%)	348 (14·6%)	295 (10·1%)	320 (12·8%)	323 (11·6%)
Unknown	181 (3·4%)	111 (4·7%)	70 (2·4%)	104 (4·1%)	77 (2·8%)

(Table 1 continues on next page)

To explore whether the effect of one surgery is different in patients undergoing one and not the other, survival models with both RRM and RRSO and their interaction term were performed.

According to inclusion criteria of the study, patients could receive *BRCA* testing any time before, at, or after breast cancer diagnosis. To account for potential lead time bias (ie, patients had to survive to receive *BRCA* testing), sensitivity analyses were performed. First, only patients tested for *BRCA* before or at breast cancer diagnosis were included. Second, a survival model where observation times were left truncated at the time of *BRCA* testing was performed.

To account for potential guarantee-time bias (ie, only patients with a better prognosis might receive a recommendation and be willing to undergo the procedures), a 3-year landmark analysis was conducted by including only patients alive and observed at 3 years after breast cancer diagnosis, either with or without disease recurrence. Patients undergoing RRM or RRSO in the first 3 years were considered as exposed (ie, in the RRM or RRSO group) from the beginning of the landmark.

	Overall cohort (n=5290)	No RRM group (n=2380)	RRM group (n=2910)	No RRSO group (n=2508)	RRSO group (n=2782)
(Table continued from previous page)					
Tumour grade					
1	94 (1·8%)	39 (1·6%)	55 (1·9%)	46 (1·8%)	48 (1·7%)
2	1191 (22·5%)	551 (23·2%)	640 (22·0%)	552 (22·0%)	639 (23·0%)
3	3535 (66·8%)	1480 (62·2%)	2055 (70·6%)	1651 (65·8%)	1884 (67·7%)
Unknown	470 (8·9%)	310 (13·0%)	160 (5·5%)	259 (10·3%)	211 (7·6%)
Hormone receptor status					
Negative	2795 (52·8%)	1210 (50·8%)	1585 (54·5%)	1339 (53·4%)	1456 (52·3%)
Positive	2421 (45·8%)	1111 (46·7%)	1310 (45·0%)	1113 (44·4%)	1308 (47·0%)
Unknown	74 (1·4%)	59 (2·5%)	15 (0·5%)	56 (2·2%)	18 (0·6%)
HER2 status					
Negative	4675 (88·4%)	2090 (87·8%)	2585 (88·8%)	2235 (89·1%)	2440 (87·7%)
Positive	377 (7·1%)	166 (7·0%)	211 (7·3%)	155 (6·2%)	222 (8·0%)
Unknown	238 (4·5%)	124 (5·2%)	114 (3·9%)	118 (4·7%)	120 (4·3%)
Tumour subtype*					
HER2-positive	377 (7·1%)	166 (7·0%)	211 (7·3%)	155 (6·2%)	222 (8·0%)
Triple-negative breast cancer	2596 (49·1%)	1130 (47·5%)	1466 (50·4%)	1252 (49·9%)	1344 (48·3%)
Luminal B-like	1172 (22·2%)	505 (21·2%)	667 (22·9%)	557 (22·2%)	615 (22·1%)
Luminal A-like	726 (13·7%)	323 (13·6%)	403 (13·8%)	333 (13·3%)	393 (14·1%)
Unknown	419 (7·9%)	256 (10·8%)	163 (5·6%)	211 (8·4%)	208 (7·5%)
Treatment					
Breast surgery for primary tumour resection					
None	15 (0·3%)	12 (0·5%)	3 (0·1%)	11 (0·4%)	4 (0·1%)
Conservative	2044 (38·6%)	1197 (50·3%)	847 (29·1%)	950 (37·9%)	1094 (39·3%)
Mastectomy	3147 (59·5%)	1103 (46·3%)	2044 (70·2%)	1478 (58·9%)	1669 (60·0%)
Unknown	84 (1·6%)	68 (2·9%)	16 (0·5%)	69 (2·8%)	15 (0·5%)
Chemotherapy use					
No	401 (7·6%)	213 (8·9%)	188 (6·5%)	229 (9·1%)	172 (6·2%)
Yes	4860 (91·9%)	2156 (90·6%)	2704 (92·9%)	2259 (90·1%)	2601 (93·5%)
Unknown	29 (0·5%)	11 (0·5%)	18 (0·6%)	20 (0·8%)	9 (0·3%)
Type of chemotherapy†					
Anthracycline and taxane-based	3422 (70·4%)	1373 (63·7%)	2049 (75·8%)	1651 (73·1%)	1771 (68·1%)
Anthracycline-based	901 (18·5%)	519 (24·1%)	382 (14·1%)	358 (15·8%)	543 (20·9%)
Taxane-based	243 (5·0%)	117 (5·4%)	126 (4·7%)	117 (5·2%)	126 (4·8%)
Other	152 (3·1%)	76 (3·5%)	76 (2·8%)	65 (2·9%)	87 (3·3%)
Unknown	142 (2·9%)	71 (3·3%)	71 (2·6%)	68 (3·0%)	74 (2·8%)
Endocrine therapy‡					
No	120 (5·0%)	42 (3·8%)	78 (6·0%)	49 (4·4%)	71 (5·4%)
Yes	2274 (93·9%)	1056 (95·0%)	1218 (93·0%)	1048 (94·2%)	1226 (93·7%)
Unknown	27 (1·1%)	13 (1·2%)	14 (1·1%)	16 (1·4%)	11 (0·8%)

(Table 1 continues on next page)

Russian Ministry of Health, Moscow, Russia (A Parokonnaya MD); **Hospital Moinhos de Vento, Porto Alegre, Brazil** (G Werutsky MD); **Hoshi General Hospital, Koriyama, Japan** (M Okano MD); **Fukushima Medical University, Fukushima, Japan** (M Okano); **Cairo Cure Oncology Center, Cairo, Egypt** (H A Azim Jr MD); **SALUS Hospital, Tirana, Albania** (K Mati MD); **Department of Population Health Sciences, Weill Cornell Medicine, New York, NY, USA** (S Rosenberg ScD); **Division of Biostatistics, Dana-Farber Cancer Institute, Boston, MA, USA** (R Gelber PhD); **Department of Medical Oncology, Clinica di Oncologia Medica, IRCCS Ospedale Policlinico San Martino, Genova, Italy** (M Lambertini PhD); **Department of Internal Medicine and Medical Specialties, School of Medicine, University of Genova, Genova, Italy** (M Lambertini)

Correspondence to:
Dr Matteo Lambertini, Department of Medical Oncology, Clinica di Oncologia Medica, IRCCS Ospedale Policlinico San Martino, 16132 Genova, Italy
matteo.lambertini@unige.it

	Overall cohort (n=5290)	No RRM group (n=2380)	RRM group (n=2910)	No RRSO group (n=2508)	RRSO group (n=2782)
(Table continued from previous page)					
Type of endocrine therapy§					
Tamoxifen alone	874 (38·4%)	476 (45·1%)	398 (32·7%)	430 (41·0%)	444 (36·2%)
Tamoxifen plus LHRHa	612 (26·9%)	311 (29·5%)	301 (24·7%)	349 (33·3%)	263 (21·5%)
LHRHa alone	48 (2·1%)	23 (2·2%)	25 (2·1%)	20 (1·9%)	28 (2·3%)
Aromatase inhibitor plus LHRHa	380 (16·7%)	114 (10·8%)	266 (21·8%)	178 (17·0%)	202 (16·5%)
Tamoxifen followed by aromatase inhibitor	310 (13·6%)	112 (10·6%)	198 (16·3%)	51 (4·9%)	259 (21·1%)
Other	31 (1·4%)	12 (1·1%)	19 (1·6%)	9 (0·9%)	22 (1·8%)
Unknown	19 (0·8%)	8 (0·8%)	11 (0·9%)	11 (1·0%)	8 (0·7%)

Data are n (%) or median (IQR). RRM=risk-reducing mastectomy. RRSO=risk-reducing salpingo-oophorectomy. LHRHa=luteinising hormone-releasing hormone agonist. *Immunohistochemistry-defined tumour subtypes are as follow: luminal A-like (oestrogen receptor-positive and progesterone receptor-positive, HER2-negative, low or intermediate grade), luminal B-like (oestrogen receptor-positive or progesterone receptor-positive, HER2-negative, high grade), triple-negative (oestrogen receptor-negative, progesterone receptor-negative, HER2-negative), or HER2-positive (any oestorgen receptor and progesterone receptor status, HER2-positive). †Calculated among patients who received chemotherapy. ‡Calculated among patients with hormone receptor-positive breast cancer. §Calculated among patients with hormone receptor-positive breast cancer who received endocrine therapy.

Table 1: **Baseline characteristics**

See Online for appendix

To avoid exclusion of missing cases, single imputation, assuming monotone missing patterns and using the logistic regression method, was performed on variables with less than 10% of missingness. If there were more than 10% of missing values, unknown category was created to combine all patients with missing covariate value.

All statistical analyses were 2-sided with $p<0·05$ considered significant, and analyses were performed using SAS (version 9.4) and R (version 4.3.3).

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between Jan 1, 2000, and Dec 31, 2020, 5660 eligible patients from 109 centres in five continents were identified, of whom 5290 were included in the present analysis (figure 1). Of 5290 patients, 3361 (63·5%) were *BRCA1* carriers, 2708 (51·2%) had node-negative, and 2421 (45·8%) had hormone receptor-positive breast cancer (table 1). Median age at breast cancer diagnosis in the entire cohort was 35 years (IQR 31–38).

Following breast cancer diagnosis, out of 5290 patients, 2910 (55·0%) underwent RRM and 2782 (52·6%) RRSO. Among the 5290 patients, 1804 (34·1%) underwent both procedures.

Among patients who underwent RRM, median age at RRM was 36·6 years (IQR 33·0–39·6; appendix p 2). Median time from breast cancer diagnosis to RRM was 0·8 years (IQR 0·5–2·7; appendix p 2). Median follow-up after RRM was 5·1 years (IQR 2·7–8·3). Among patients who underwent RRSO, median age at RRSO was 39·7 years (IQR 37·4–41·8; appendix p 2). Median time from breast cancer diagnosis to RRSO was 3·0 years (IQR 1·3–6·8; appendix p 2). Median follow-up after RRSO was 4·9 years (IQR 2·3–8·1).

At a median follow-up of 8·2 years (IQR 4·7–12·8), out of 5290 patients, 686 (13·0%) had died, 1923 (36·4%) had experienced a disease-free survival event, and 1751 (33·1%) had experienced a breast cancer-free interval event (appendix p 3).

RRM was associated with a significantly better overall survival (unadjusted HR 0·62, 95% CI 0·52–0·73; adjusted HR [aHR] 0·65, 95% CI 0·53–0·78; 20-year restricted mean overall survival time 17·89 years [95% CI 17·61–18·17] with RRM *vs* 16·65 years [16·38–16·92] without RRM; average gain of 1·24 years at 20 years after breast cancer diagnosis; appendix p 4, figure 2A). This association was observed irrespective of the specific *BRCA* gene, age at breast cancer diagnosis, tumour subtype, tumour size, nodal status, chemotherapy use, and timing of *BRCA* testing (table 2).

RRSO was associated with a significantly better overall survival (unadjusted HR 0·67, 95% CI 0·57–0·80; aHR 0·58, 95% CI 0·48–0·71; 20-year restricted mean overall survival time 17·73 years [95% CI 17·43–18·03] with RRSO *vs* 16·67 years [16·38–16·96] without RRSO; average gain of 1·06 years at 20 years after breast cancer diagnosis; appendix p 5, figure 3A). This association was observed irrespective of age at breast cancer diagnosis, tumour size, nodal status, chemotherapy use, and timing of *BRCA* testing. A significant interaction was observed according to specific *BRCA* gene (*BRCA1* carriers: aHR 0·44, 95% CI 0·34–0·57; *BRCA2* carriers: 0·86, 0·64–1·15; $p_{interaction}=0·0005$) and tumour subtype (triple-negative: aHR 0·44, 95% CI 0·33–0·58; luminal-like: 0·80, 0·60–1·05, and HER2-positive: 0·50, 0·25–0·98; $p_{interaction}=0·0086$; table 3).

Patterns of first disease-free survival events according to RRM uptake are reported in the appendix (p 3). Patients undergoing RRM experienced a lower incidence of second

primary breast cancers as first event (2·57 events per 100 person-years for no RRM *vs* 0·32 events per 100 person-years for RRM). RRM was associated with significantly improved disease-free survival (aHR 0·58, 95% CI 0·52–0·65; average gain of 4·08 years at 20 years after breast cancer diagnosis; appendix p 4; figure 2B), breast cancer-free interval (aHR 0·55, 95% CI 0·48–0·62; average gain of 4·39 years at 20 years after breast cancer diagnosis; appendix p 4; figure 2C) and reduced incidence of second primary breast cancers (aHR 0·44 95% CI 0·37–0·52; average gain of 4·65 years at 20 years after breast cancer diagnosis; appendix p 4; figure 2D).

Patterns of first disease-free survival events according to RRSO uptake are reported in the appendix (p 3). Patients undergoing RRSO experienced a lower risk of developing ovarian or fallopian tube cancers (0·37 events per 100 person-year for no RRSO *vs* 0·05 events per 100 person-years for RRSO) and fewer second primary breast cancers (2·03 events per 100 person-years for no RRSO *vs* 1·03 events per 100 person-years for RRSO). RRSO was associated with improved disease-free survival (aHR 0·68, 95% CI 0·61–0·77; average gain of 2·92 years at 20 years after breast cancer diagnosis; appendix p 5, figure 3B), breast cancer-free interval (aHR 0·65, 95% CI 0·57–0·74; average gain of 2·93 years at 20 years after breast cancer diagnosis; appendix p 5, figure 3C), and reduced incidence of ovarian or fallopian tube cancers (aHR 0·44, 95% CI 0·25–0·77; average gain of 0·83 years at 20 years after breast cancer diagnosis; appendix p 5, figure 3D).

No significant interaction was observed between RRM and RRSO on overall survival ($p_{interaction}$=0·83), suggesting that the effect of RRM and RRSO were independent (appendix p 6). Conversely, a significant interaction was observed in breast cancer-free interval ($p_{interaction}$=0·0063); the p value for interaction was 0·054 in disease-free survival. Thus, the effect of RRSO on disease-free survival and breast cancer-free interval was more pronounced among patients undergoing also RRM (appendix p 6).

Results of the sensitivity analyses were consistent with those of the main analysis. When including only patients

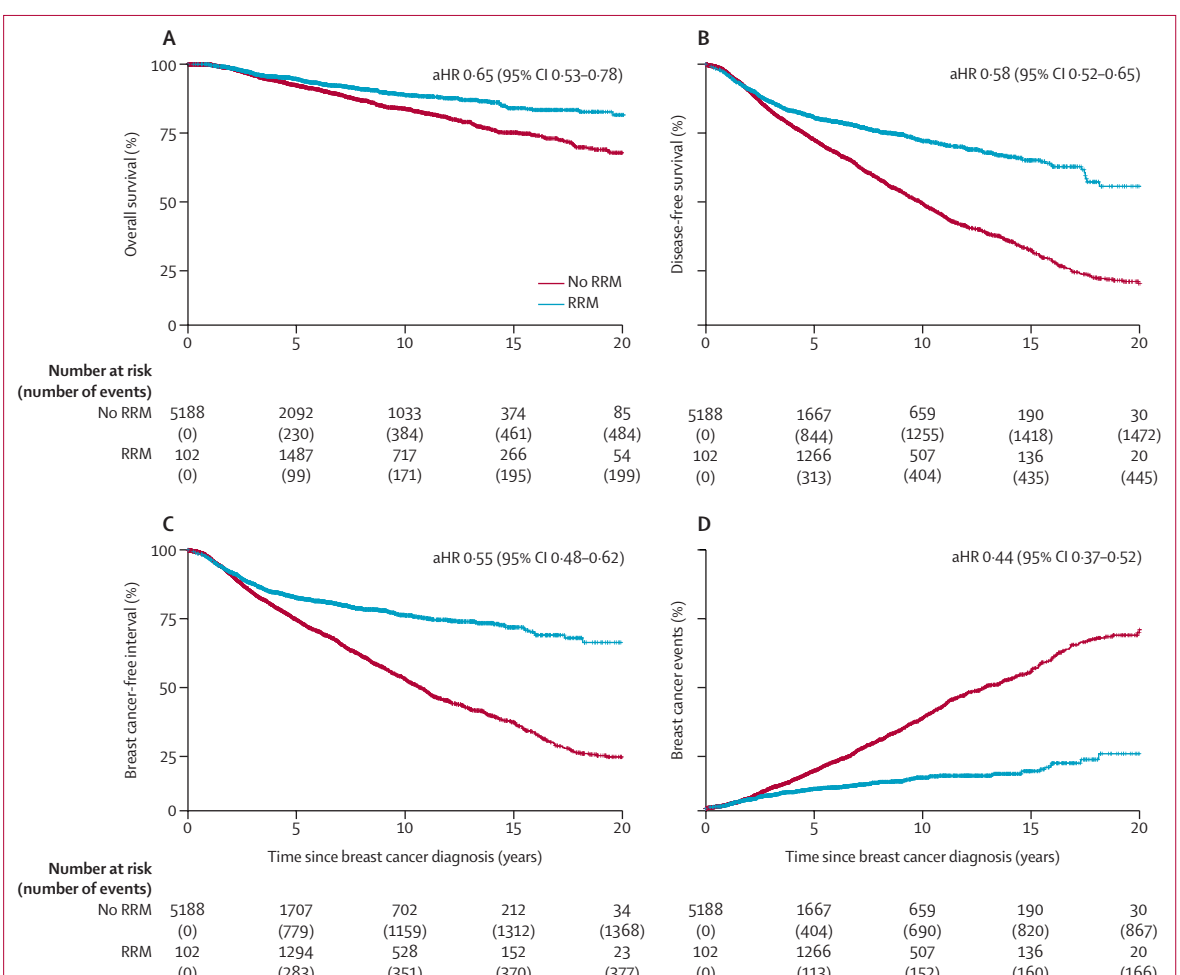

Figure 2: **Survival curves for the association between RRM and overall survival (A), disease-free survival (B), breast cancer-free interval (C), and breast cancer events (D)**

aHR=adjusted hazard ratio. RRM=risk-reducing mastectomy. Numbers in brackets represent the number of patients with a survival event at different timepoints.

	Unadjusted HR (95% CI)	$p_{interaction}$	Adjusted HR* (95% CI)	$p_{interaction}$
Specific *BRCA* gene	..	0·89	..	0·60
BRCA1	0·61 (0·50–0·75)	..	0·67 (0·53–0·85)	..
BRCA2	0·63 (0·48–0·83)	..	0·60 (0·44–0·83)	..
Age at breast cancer diagnosis, years	..	0·31	..	0·87
≤30	0·70 (0·50–0·97)	..	0·66 (0·45–0·97)	..
31–35	0·52 (0·39–0·69)	..	0·68 (0·50–0·93)	..
36–40	0·67 (0·52–0·86)	..	0·61 (0·45–0·82)	..
Tumour subtypes	..	0·77	..	0·71
Luminal-like	0·64 (0·50–0·83)	..	0·63 (0·47–0·85)	..
Triple-negative breast cancer	0·59 (0·47–0·74)	..	0·63 (0·49–0·82)	..
HER2-positive	0·72 (0·39–1·32)	..	0·85 (0·44–1·66)	..
Tumour size	..	0·40	..	0·34
T1	0·76 (0·56–1·04)	..	0·60 (0·43–0·83)	..
T2	0·59 (0·46–0·74)	..	0·68 (0·52–0·89)	..
T3–4	0·63 (0·44–0·89)	..	0·90 (0·58–1·38)	..
Nodal status	..	0·037	..	0·17
N0	0·54 (0·41–0·72)	..	0·54 (0·40–0·73)	..
N1	0·82 (0·64–1·04)	..	0·76 (0·59–0·99)	..
N2–3	0·51 (0·35–0·74)	..	0·56 (0·38–0·84)	..
Chemotherapy use	..	0·41	..	0·96
Yes	0·61 (0·51–0·72)	..	0·65 (0·53–0·79)	..
No	0·81 (0·42–1·57)	..	0·66 (0·33–1·32)	..
Timing of *BRCA* testing	..	0·72	..	0·62
Tested before or at diagnosis	0·58 (0·45–0·74)	..	0·65 (0·48–0·89)	..
Tested after diagnosis	0·62 (0·48–0·80)	..	0·59 (0·44–0·78)	..
Income	..	0·43	..	0·65
Low–middle	0·49 (0·25–0·93)	..	0·64 (0·33–1·25)	..
High	0·63 (0·53–0·75)	..	0·75 (0·63–0·90)	..

HR=hazard ratio. *Survival models were stratified for year at breast cancer diagnosis, region or country, and nodal status and were adjusted for the development of distant recurrence or second primaries as time-dependent covariates.

Table 2: **Subgroup analyses for the association of risk-reducing mastectomy with overall survival**

tested for *BRCA* before or at diagnosis (n=2581), the aHR were 0·61 (95% CI 0·42–0·88) for RRM and 0·70 (0·49–1·01) for RRSO. When accounting for the delayed entry (ie, left truncation at the time of *BRCA* testing), consistently better overall survival results were observed for both RRM (aHR 0·54, 95% CI 0·44–0·66) and RRSO (aHR 0·47, 95% CI 0·38–0·58).

Similarly, in the 3-year landmark analysis that included only patients alive and observed at 3 years after breast cancer diagnosis, either with or without disease recurrence (n=4474), overall survival was significantly improved for both RRM (aHR 0·57, 95%CI 0·45–0·71) and RRSO (aHR 0·58, 95% CI 0·47–0·72).

Discussion

This global study provides evidence on the association between risk-reducing surgeries and survival outcomes among young *BRCA* carriers with a previous history of breast cancer. Our results suggest that undergoing RRM, RRSO, or both procedures, was associated with improved survival outcomes in this clinical setting. The favourable effect of RRM was observed irrespective of the specific *BRCA* gene, whereas the protective effect of RRSO was more pronounced among *BRCA1* carriers.

Existing guidelines recommend that different factors should be considered in the counselling of *BRCA* carriers for assessing the risk of contralateral breast cancer and the indication for RRM. In our cohort, more than half of the patients opted for RRM with a median time of less than 1 year from breast cancer diagnosis to RRM. Notably, more patients treated in high-income countries underwent RRM as compared with those from low-income and middle-income countries (2677 of 4584 [58·4%] *vs* 233 of 706 [33·0%]), with the highest uptake in north America (480 of 629, 76·3%). The finding that patients undergoing RRM were more likely to receive *BRCA* testing results either before or at breast cancer diagnosis than afterwards (59·0% *vs* 34·7%) suggests that the availability of *BRCA* test result at the time of surgical decision making for the primary tumour might affect patients' willingness to undertake surgery on both the affected and healthy breasts simultaneously. The median time from breast cancer diagnosis to RRM, which was less than 1 year, could be due to the different timing and expansion of *BRCA* testing over time, particularly among women diagnosed with breast cancer at a young age.[3,17]

Previous studies showed that RRM reduces the risk of contralateral breast cancer, with no apparent effect on overall survival.[3,26,27] However, little evidence exists to counsel young women with breast cancer, who have been under-represented in previous studies. Acquiring this information is particularly relevant in these patients considering that young age at diagnosis of breast cancer is in itself associated with an increased risk of developing second primary breast cancers.[28,29] One previous study reported a subgroup analysis according to age at breast cancer diagnosis, with an observed greater benefit of RRM among young patients versus older patients, but the sample size was small (n=267).[13] Our results, based on a cohort of more than 5000 young *BRCA* carriers with history of breast cancer, suggest that RRM was associated with significantly improved survival outcomes irrespective of patient and tumour characteristics.

According to recent guidelines, a different age cutoff is recommended for RRSO in different *BRCA* carriers, beginning at age 35–40 years for *BRCA1* carriers and 40–45 years for *BRCA2* carriers.[3,29] This age-based recommendation is supported by the different age of ovarian cancer onset and the specific risk conferred by each specific *BRCA* gene.[2] Median age at RRSO in our study did not differ according to specific *BRCA* gene (39·5 years in *BRCA1* carriers *vs* 40·0 years in *BRCA2* carriers) reflecting the lack of a clear age-based recommendation in this regard at the time of patient inclusion in our study. Considering the implications of RRSO on the reproductive window and quality of life of young *BRCA* carriers,[30] appropriate counselling is particularly challenging, and even more in patients who

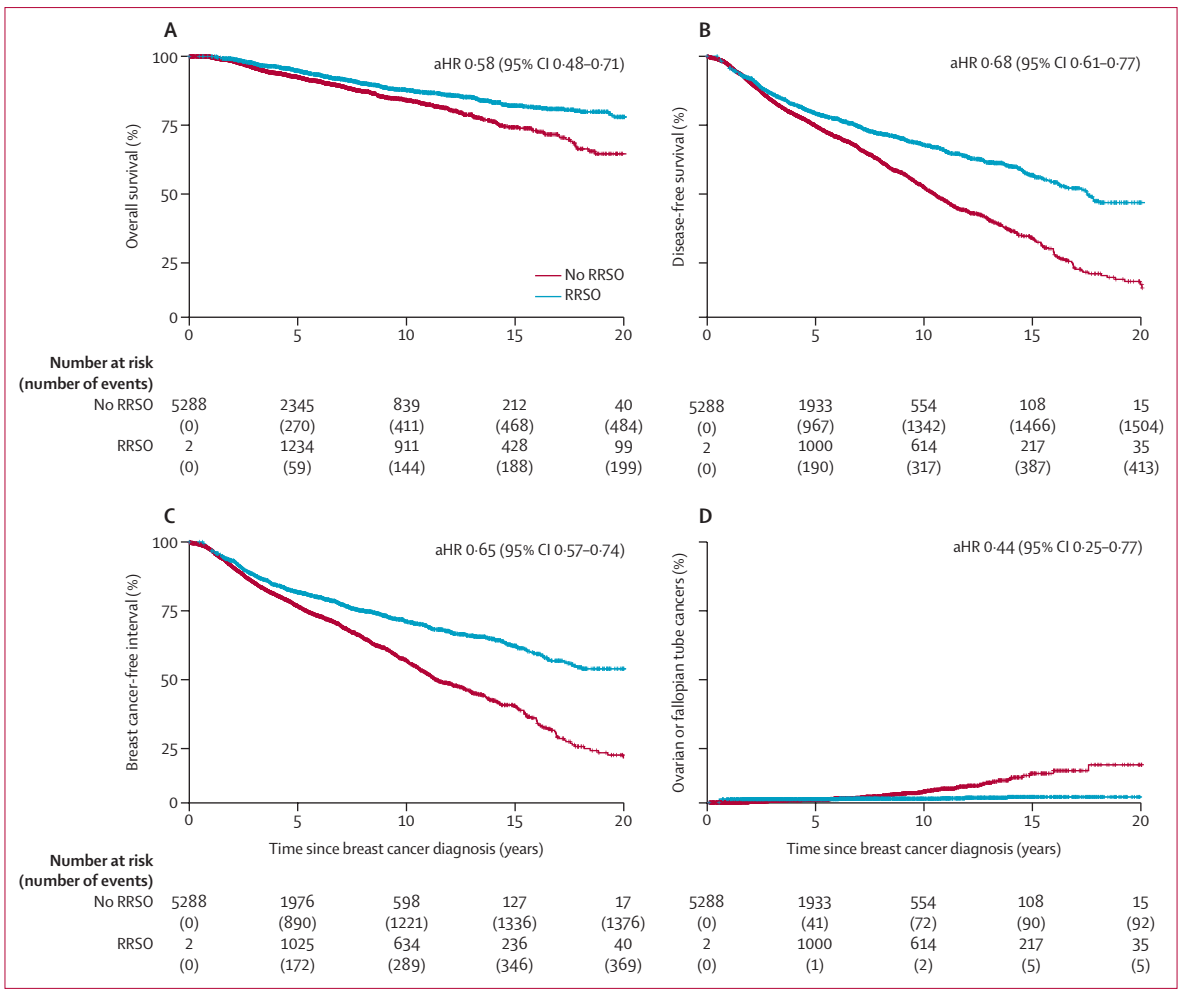

Figure 3: **Survival curves for the association between RRSO and overall survival (A), disease-free survival (B), breast cancer-free interval (C) and ovarian or fallopian tube cancer events (D)**

aHR=adjusted hazard ratio. RRSO=risk-reducing salpingo-oophorectomy. Numbers in brackets represent the number of patients with a survival event at different timepoints.

cannot undergo hormone replacement therapy due to a previous history of breast cancer.

Two previous studies have investigated the association of RRSO with survival in patients with a personal history of breast cancer.[7,16] Both studies showed better survival outcomes in patients undergoing RRSO; however, no specific data for counselling specifically young patients were reported, one study had a small sample size (n=676)[16], and the other included both *BRCA* healthy carriers and those with previous history of breast cancer.[7] In our study, we observed an important beneficial effect of RRSO in young *BRCA* carriers with previous breast cancer. By including a large sample size of patients, of whom 1891 were *BRCA2* carriers, we observed a significant interaction in the subgroup analysis according to specific *BRCA* gene, with a greater benefit associated with RRSO in *BRCA1* carriers (aHR 0·44) than in *BRCA2* carriers (aHR 0·86). These findings could be partially explained by the lower risk of ovarian cancer among *BRCA2* carriers, the young age of our population, and the relatively short follow-up. The significant interaction observed according to tumour subtype could be attributed to the specific *BRCA* gene considering the different risk of developing different tumour subtypes in *BRCA1* and in *BRCA2* carriers.[22] Notably, most of the patients with hormone receptor-positive disease received adjuvant endocrine therapy, which is known to reduce also the risk of second primary breast cancers.[3,17]

In our study, RRM and RRSO were associated with improvements in both disease-free survival and breast cancer-free interval. Patterns of first disease-free survival events according to the uptake of RRM or RRSO were in line with the expected reduction in the risk of developing breast and ovarian cancers.[6,7,11,13] Specifically, RRM and RRSO more than halved the risk of developing second primary breast cancers and ovarian or fallopian tube cancers, respectively. RRSO was also associated with reduced second primary breast cancer risk. However, by

	Unadjusted HR (95%CI)	$p_{interaction}$	Adjusted HR* (95%CI)	$p_{interaction}$
Specific *BRCA* gene	..	<0·0001	..	0·0005
BRCA1	0·44 (0·35–0·56)	..	0·44 (0·34–0·57)	..
BRCA2	1·25 (0·96–1·61)	..	0·86 (0·64–1·15)	..
Age at breast cancer diagnosis, years	..	0·77		0·68
≤30	0·71 (0·45–1·14)	..	0·46 (0·27–0·78)	..
31–35	0·70 (0·53–0·94)	..	0·58 (0·42–0·81)	..
36–40	0·62 (0·49–0·80)	..	0·59 (0·45–0·78)	..
Tumour subtypes	..	<0·0001	..	0·0086
Luminal-like	1·06 (0·83–1·35)	..	0·80 (0·60–1·05)	..
Triple-negative breast cancer	0·43 (0·33–0·56)	..	0·44 (0·33–0·58)	..
HER2-positive	0·72 (0·39–1·31)	..	0·50 (0·25–0·98)	..
Tumour size	..	0·27	..	0·44
T1	0·83 (0·60–1·13)	..	0·68 (0·48–0·96)	..
T2	0·61 (0·48–0·77)	..	0·58 (0·45–0·77)	..
T3–4	0·75 (0·53–1·06)	..	0·48 (0·31–0·74)	..
Nodal status	..	0·32	..	0·086
N0	0·56 (0·42–0·76)	..	0·45 (0·33–0·61)	..
N1	0·75 (0·58–0·96)	..	0·70 (0·54–0·91)	..
N2–3	0·71 (0·50–0·998)	..	0·60 (0·42–0·85)	..
Chemotherapy use	..	0·20	..	0·098
Yes	0·65 (0·55–0·78)	..	0·55 (0·45–0·68)	..
No	1·03 (0·53–2·00)	..	1·04 (0·51–2·10)	..
Timing of *BRCA* testing	..	0·22	..	0·57
Tested before or at diagnosis	0·59 (0·44–0·77)	..	0·61 (0·44–0·85)	
Tested after diagnosis	0·73 (0·58–0·92)	..	0·54 (0·42–0·71)	
Income	..	0·39	..	0·81
Low–middle	0·84 (0·51–1·39)	..	0·69 (0·41–1·15)	..
High	0·66 (0·55–0·80)	..	0·64 (0·53–0·78)	..

HR=hazard ratio. *Survival models were stratified for year at breast cancer diagnosis, region or country, and nodal status and were adjusted for the development of distant recurrence or second primaries as time-dependent covariate.

Table 3: **Subgroup analyses for the association of risk-reducing salpingo-oophorectomy with overall survival**

considering RRM and RRSO separately, we cannot rule out the possibility that patients who underwent one type of risk-reducing surgery were also more likely to undergo the other procedure (34·1% of the patients underwent both surgeries). In survival models exploring the association of both RRM and RRSO on survival outcomes, no interaction was observed in overall survival. However, for disease-free survival and breast cancer-free interval, an interaction was observed. In the interpretation of these results, the high incidence of second primary breast cancers in this population should be considered;[29] hence, patients who did not undergo RRM were at risk of developing a second primary breast cancer, which counts as an event for disease-free survival and breast cancer-free interval, before having the opportunity to undergo RRSO. This might partially explain the greater survival benefit observed in patients who underwent both RRM and RRSO.

Our study has several limitations that need to be considered. First, this is a retrospective observational study including 109 centres from five continents with different health-care systems and patients treated over a period of 20 years, during which indications for *BRCA* testing as well as those for RRM and RRSO have changed. During this period, neoadjuvant immunotherapy, adjuvant CDK4/6 inhibitors, or olaparib were not yet standard of care. No information on patients' perception and acceptability nor on quality of life was collected. Moreover, patients who did and did not choose to undergo RRM, RRSO, or both procedures, might have had a different perceived risk of second primary breast and ovarian cancers as well as guarantee time bias, with a consequent risk of overestimating the survival benefit of these strategies. However, the analyses adjusting for time to recurrence in overall survival models and the 3-year landmark analysis provided consistent results. Since time from breast cancer diagnosis to *BRCA* testing was not an inclusion criterion, patients might have been subjected to lead time bias (ie, patients have to survive to receive *BRCA* testing). However, by including only patients tested before or at diagnosis and using survival models with left truncation of observation times, consistent results were observed. In addition, by including a time-varying covariate in a Cox regression model, the ability to infer about the association of the effect of the covariate on the incidence of outcome might be lost;[31] therefore, our findings should be interpreted with caution. However, considering that our results showed a reduction of the instantaneous hazard for all survival outcomes, although we cannot formally quantify it, it is probable that this translated into a clinical benefit. Finally, we acknowledge that the highest level of evidence would come from a randomised trial, sensitivity analyses do not provide absolute guarantees, and a target trial emulation approach could further support our findings. However, given the complexities of conducting a randomised trial to address this question in such a specific patient population, we believe that our study with its global representation and methodology provides unique evidence in this field.

In conclusion, in this large international cohort of *BRCA* carriers with previous breast cancer diagnosis at a young age, RRM and RRSO were both associated with beneficial effect on survival outcomes. These findings provide evidence for a tailored counselling of a unique and high-risk patient population on cancer-risk management strategies. Future research should focus on long-term follow-up and patient-centred outcomes, including quality of life and reproductive considerations, to optimise shared decision-making processes.

Contributors

EB, ASo, LB, and MLa contributed to study's conceptualisation, data curation, formal statistical analysis, and drafting of the original and revised versions of the manuscript. SR and RG also contributed to data curation and formal statistical analysis. MLa was involved in funding acquisition. All authors contributed to acquisition and interpretation of the data, methodology, project administration, and review and editing of the manuscript. All authors had full access to all of the data in the study, take responsibility for the integrity of the data and accuracy of the analysis. All authors had final responsibility for the decision to submit for publication.

Declaration of interests

EB reports speakers fees from Eli Lilly and research funding (to their institution) from Gilead, outside the submitted work. ASo reports consulting or advisory roles for Eli Lilly, Novartis, Roche, and Stemline; travel, accommodations, and expenses from Roche and Pfitzer; speakers bureau at Roche, Novartis, Stemline, Progenetics, Gilead, and MSD; and grant support from Novartis, Roche, and Gilead, outside the submitted work. EA reports speakers honoraria from Eli Lilly, AstraZeneca, Bayer, and Abscint; advisory role for AstraZeneca; research grant (to their institution) from Gilead; and meeting or travel grants from Eli Lilly, Daiichi Sankyo, AstraZeneca, Menarini, and Abscint, outside the submitted work. 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Data sharing

Deidentified individual patient data, data dictionary, and statistical analysis plan will be available for 5 years after publication upon reasonable request to the corresponding author (matteo.lambertini@unige.it), after proper revision of the data transfer agreement of each participating centre and if ultimately allowed by local ethics committees.

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