Review

Risk Reduction and Survival Benefit of Risk-Reducing Salpingo-oophorectomy in Hereditary Breast Cancer: Meta-analysis and Systematic Review

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Abstract

We performed a meta-analysis to examine the relationship between risk-reducing salpingo-oophorectomy (RRSO) and breast cancer (BC) risk and mortality. RRSO was associated with a significant reduction in the incidence of BC in women with *BRCA1/2* mutations, regardless of history of BC. RRSO could improve the survival of women with BC.

Background: Objections have been raised to performing risk-reducing salpingo-oophorectomy (RRSO) to reduce disease incidence and mortality of women with *BRCA* mutations. We aimed to examine the relationship between RRSO and breast cancer (BC) risk and mortality with a meta-analysis. **Materials and Methods:** We conducted a comprehensive literature search using the PubMed and Embase databases for literature published from these databases' creation to September 2017. Hazard ratio (HR) estimates were identified directly from the original articles. Pooled results were calculated on the basis of nonoverlapping studies by fixed-effect meta-analysis. **Results:** RRSO was associated with a significant reduction in the incidence of BC in women with *BRCA1/2* mutations who had no history of BC (HR = 0.58; 95% confidence interval [CI], 0.37 to 0.78). Even in women with a history of BC, RRSO could reduce the risk of recurrence (HR = 0.50; 95% CI, 0.31 to 0.69). We further found that publication year was a critical interaction factor from a corresponding subgroup analyses in BC risk ($P_{heterogeneity}$ = .024). In addition, we found that RRSO could improve the survival of women with BC (HR = 0.33; 95% CI, 0.28 to 0.38). **Conclusion:** Summary estimates presented here indicate that RRSO was closely related to the reduced risk of BC caused by *BRCA* mutations, but publication year was a critical interaction factor and it should be noted that more recent studies have failed to find a significant reduction in BC risk associated with RRSO.

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Introduction

Breast cancer (BC) is one of the most common cancer diseases in women.[1,2] Ten percent to 20% of women diagnosed with advanced BC have a poor survival rate.[3] The *BRCA1* or *BRCA* mutation increase the risk of BC by 50% to 80%.[4-6]

Risk-reducing surgery has been proposed to improve the survival of BC patients or to prevent BC incidence for subjects who once were clinically identified as having a *BRCA* gene mutation by DNA direct sequencing or family history. Meanwhile, many studies have been conducted on whether risk-reducing salpingo-oophorectomy (RRSO), one of the most common risk-reducing surgeries, could reduce the risk of BC in women with *BRCA* gene mutation.

In a recent meta-analysis, Li et al[7] suggested that RRSO can reduce the risk of BC to 45% in women who have *BRCA* mutations and who have no history of BC. In the PROSE study, a large multicenter cohort study, women with *BRCA* gene mutation who underwent RRSO had a significantly lower BC risk in 50% compared to those who did not receive RRSO, a finding comparable to previous studies.[8] Nevertheless, Kotsopoulos et al[9] suggested that

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no significant statistical relationship could be found between RRSO and survival outcomes among patients with *BRCA* mutations in what is to date the largest prospective analysis. Likewise, Heemskerk-Gerritsen et al[10] obtained results indicating that there were no significant associations between RRSO and BC risk. All the women in these studies had no history of BC, but the last 2 studies had findings different from the first 2, which may be related to sample size, type of gene mutation, or proportion of RRSO patients. All in all, we observed that RRSO had a greater significance for women with a history of BC and women with the *BRCA1* mutation.

The same disagreements also exist between RRSO and BC mortality. So far, most studies have shown that women who receive RRSO have significantly improved survival, but some researchers have also observed that the results were different according to different genotypes. Domchek et al[11] and Metcalfe et al[12] indicated that RRSO was more helpful for women with *BRCA1*-positive disease and had no protective effect for women with *BRCA2*-positive disease. However, this difference was not observed in the study of Finch et al.[13] The impact of genotype on mortality of BC after patients undergo RRSO thus needs to be further explored. Li et al[7] concluded that RRSO reduced all-cause mortality for women without a history of BC, with a rate of 23% compared to 34% of those with a history of BC before RRSO. In line with this, Domchek et al[11] reported that there was a statistically significant reduction in BC-specific mortality if RRSO was performed on women with a history of BC. It thus seems likely that a history of BC before RRSO is a factor affecting BC mortality.

Therefore, in order to explore the relationships between a history of BC and type of mutation with, respectively, the incidence and mortality of BC, we carried out a systematic review that assessed 13 years' worth of related research. We found several articles that suggested that RRSO is not exactly significant in terms of BC risk and mortality.

Materials and Methods

Search Strategy

This systematic review and meta-analysis was reported and carried out according to the PRISMA guidelines.[14] We conducted a comprehensive electronic literature search on the Medline (via PubMed) and Embase (via Embase) databases using the search terms "*BRCA1*," "*BRCA2*," "oophorectomy," and "breast cancer," updated to November 26, 2017. Details are listed in Supplemental Table 1 in the online version.

We also manually reviewed the references lists of previous reviews for relevant articles. Only studies written in the English language were included in this meta-analysis. We did not attempt to obtain any unpublished studies. Any disagreement regarding study inclusion was resolved by discussion.

All procedures performed in studies involving human participants were in accordance with the ethical standards of institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or with comparable ethical standards. Informed consent was obtained from all individual participants included in the studies we analyzed.

Study Selection

Two investigators (Y.L.X. and K.W.) independently screened titles and abstracts of the identified articles to assess eligibility. Then the 2 investigators independently evaluated the articles after reviewing the full text. When two or more publications were of the same study, those with the larger sample and more detailed data were adopted. Any inconsistencies were resolved by further discussion.

Articles were included in our study if they fulfilled all of the following criteria: (1) Both the case and control subjects were women who had *BRCA1* or *BRCA2* mutations, regardless of history of BC before surgery. (2) The case subjects were treated with prophylactic surgeries, including oophorectomy and salpingo-oophorectomy. (3) The control subjects were women who did not undergo these surgeries. (4) BC risk or mortality due to prophylactic surgeries for women with and without a history of BC, and hazard ratio (HR) values were provided. (5) Study type was a cohort study or a case—control study.

Data Extraction and Quality Assessment

Data extraction was implemented independently by one investigator (Y.L.X.), and then its accuracy was checked by another investigator (K.W.). Any inconsistency was resolved by discussion. The following information was extracted from each study: first author's family name, year of publication, data source, type of study, mean follow-up duration, mean age at diagnosis BC, history of BC (sample size), number of each mutation type, exposure or interventional variables, BC cases, mortality cases, HRs and/or odds ratios (ORs) and 95% confidence intervals (CIs) of BC risk, HRs and/or ORs and 95% CIs of mortality, and adjustment factors.

We used the Newcastle-Ottawa quality assessment scale to evaluate each study's quality.[15] Quality assessment included 3 aspects, including selection, comparability, and outcome. A study could get a maximum of 1 star for each point. Only 9 stars could be obtained at the highest level of each study. We considered a study with more than 7 stars to be a high-quality study, and 7 or fewer stars indicated low-quality research.

Statistical Analysis

We conducted a meta-analysis of patients with and without a history of BC, respectively, and performed subgroup analyses of women who had different *BRCA* subtypes (*BRCA1* mutation group, *BRCA2* mutation group, and group with both, denoted *BRCA1/2*). We calculated the pooled effect size for each outcome (BC risk and mortality) along with the corresponding 95% CI. HR was adopted to assess the relationship between oophorectomy (or salpingo-oophorectomy), and the BC risk and survival of BC cases. OR and relative risk were considered as equivalent to HR simultaneously when the incidence of BC or the death rate was $< 20\%$.[16-18] We calculated the overall effect estimation of all dichotomous data as the risk ratio with 95% CI.

Statistical heterogeneity among studies was evaluated by Q statistics. Here, we used $P_{\text{heterogeneity}}$ (qualitative analysis) and I^2 (quantitative analysis) to reflect the heterogeneity between studies. When $P_{\text{heterogeneity}} > .10$, we chose the fixed effect model. When

$P_{heterogeneity} \leq .10$, heterogeneity would be analyzed and processed first. If the heterogeneity still cannot be eliminated, we would choose the random-effect model. The larger the I^2 value, the greater the heterogeneity between the studies. In general, heterogeneity is classified as low, medium, and high by 25%, 50%, and 75%. To assess the possibility of publication bias, we used the Begg rank correlation test. All analyses were conducted by Stata/SE software 12.0 (StataCorp, College Station, TX). All statistical tests were 2 sided. $P < .05$ was considered statistically significant.

Results

Literature Search and Study Characteristics

The process and results of the literature search are shown in Figure 1. The search yielded 1093 studies, 580 from the PubMed database and 513 from the Embase database, between July 1994 and October 2017. After excluding 185 duplicates, we obtained 82 potentially relevant studies by screening titles and abstracts. We excluded 65 studies that did not conform to our standards after browsing full text. Detailed reasons for exclusion are listed in Supplemental Table 2 in the online version. When we reviewed the reference lists of prior reviews, we discovered 2 additional studies that were in line with the inclusion criteria. In the end we had 19 studies, the characteristics and details of which are listed in Tables 1 and 2.

The study included 9 prospective cohort studies,[9,11,13,19-23,28] 9 retrospective cohort studies,[10,12,16-18,24-26,29] and 1 case–control study.[27] Eight of these studies were from Europe, including countries such as the United Kingdom and the Netherlands.[10,18,19,21,25,26,28,29] Six studies were from the United States.[9,12,16,17,20,24] The remaining 9 studies were international cooperative studies. Including exposed and nonexposed (surgery or nonsurgery) populations, the sample size ranged from 36 to 3722. The mean or median follow-up time ranged from 2.6 to 16.5 years. The methods of determining surgical exposure varied from study to study. Most studies used questionnaires to interview or mail participants; medical records were also used. Sixteen studies had ≥ 7 stars, indicating that the quality of the included studies was generally good (Supplemental Table 3 in the online version).

Figure 1 Flowchart of Selection of Eligible Studies

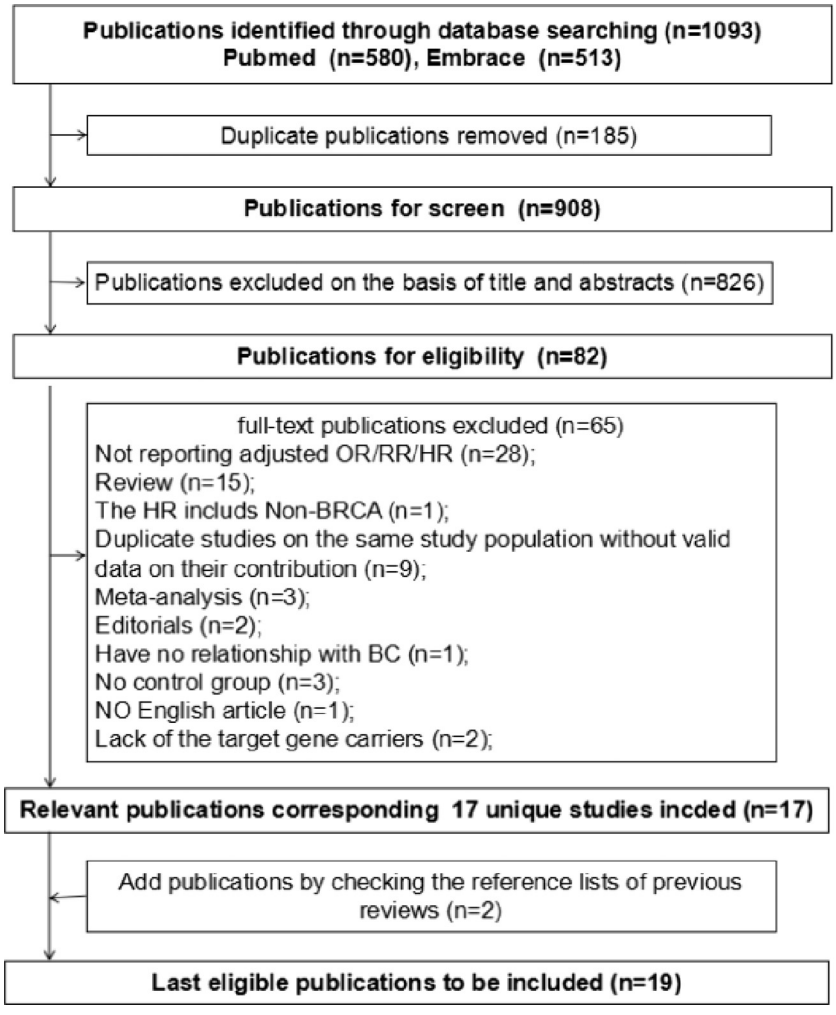


Table 1 Characteristics of 14 BC Incidence-Related Studies Included in Meta-analysis

Study	Study Design	Cohort/Data Source	Follow-up (y)	Mean Age at Diagnosis of BC (y)	BC-Free When Enrolled	Mutation Type	No. of Patients Undergoing Surgery	No. of BC Cases	Adjustment Factors
Domchek (2010)[11]	PCS	22 centers in PROSE Consortium	3.65 (median)	NA	No: 1370	*BRCA1*: 869 *BRCA2*: 501	RRSO: 336 Non-RRSO: 1034	RRSO: 39 Non-RRSO: 223	Year of birth and stratified by center
					Yes: 647	*BRCA1*: 397 *BRCA2*: 250	RRSO: 208 Non-RRSO: 439	RRSO: 23 Non-RRSO: 60	
Mavaddat (2013)[19]	PCS	EMBRACE	3.3 (mean)	44.8	No: 988	*BRCA1*: 501 *BRCA2*: 485 *BRCA1/2*: 2	RRSO: 309 Non-RRSO: 679	RRSO: 18 Non-RRSO: 46	Parity and age at first birth
			3.0 (mean)	50.8	Yes: 651 (UBC)	*BRCA1*: 340 *BRCA2*: 309 *BRCA1/2*: 2	RRSO: 315 Non-RRSO: 336	(CBC) RRSO: 23 Non-RRSO: 38	
Kramer (2005)[20]	PCS	23 self-referred and physician-referred HBOC families from National Cancer Institute	16.5 (mean)	47.3	No: 98	*BRCA1*: 98	RRSO: 33 Non-RRSO: 65	RRSO: 6 Non-RRSO: 27	NA
Moller (2002)[21]	PCS	4 European countries: Norway, Scotland, England, Holland	3.1 (mean)	NA	No: 36	NA	RRSO: 21 Non-RRSO: 15	RRSO: 1 Non-RRSO: 7	NA
Kauff (2008)[22]	PCS	MSKCC and 10 academic referral centers participating in PROSE study group	2.9 (mean)	NA	BOTH: 597	*BRCA1*: 368 *BRCA2*: 229	RRSO: 303 Non-RRSO: 294	RRSO: 19 Non-RRSO: 28	Age at start of follow-up, parity, personal history of BC, history of prior use of HRT
Kotsopoulos (2017)[9]	PCS	78 participating centers in 12 countries	5.6 (mean)	RRSO: 52.5 Non-RRSO: 42.5	No: 3722	*BRCA1*: 2969 *BRCA2*: 725 *BRCA1/2* or missing: 28	RRSO: 1552 Non-RRSO: 2170	RRSO: 143 Non-RRSO: 207	Other variables in model, age at menarche, parity, breastfeeding
Finkelman (2012)[23]	PCS	22 international centers in PROSE Consortium	RRSO: 6.5 Non-RRSO: 4.5 (mean)	RRSO: 47.9 Non-RRSO: 42.9	BOTH: 2362	*BRCA1*: 1523 *BRCA2*: 839	RRSO: 763 Non-RRSO: 1599	RRSO: 79 Non-RRSO: 317	RRSO, RRM, mutation type
Heemskerk-Gerritsen (2015)[10]	RCT	HEBON	3.2 (median)	RRSO: 50 Non-RRSO: 37	No: 822	*BRCA1*: 589 *BRCA2*: 233	RRSO: 346 Non-RRSO: 476	RRSO: 42 Non-RRSO: 47	Age
Metcalfe (2011)[17]	RCT	10 participating cancer genetics clinics	10.5 (mean)	42.4	Yes: 396 (UBC)	*BRCA1*: 254 *BRCA2*: 137 *BRCA1/2*: 5	RRSO: 255 Non-RRSO: 132 Missing: 4	NA (IBC)	Age at first cancer diagnosis, mutation status, family history, other treatments received
Metcalfe (2004)[24]	RCT	10 participating cancer genetics clinics	9.2 (mean)	42.1	Yes: 336 (UBC)	*BRCA1*: 224 *BRCA2*: 112	RRSO: 107 Non-RRSO: 229	NA (CBC)	Age, mutation, other treatments
Brekelmans (2006)[25]	RCT	Rotterdam Family Cancer Clinic	5.1 (Median)	Median: 39	Yes: 170	*BRCA1*: 170	RRSO: 55 Non-RRSO: 115	NA	Chemotherapy
Johns (2017)[16]	RCT	University of Utah and Huntsman Cancer Hospital	2.6 (Median)	NA	No: 106	NA	RRSO: 46 Non-RRSO: 60	NA	NA

Table 1 Continued

Study	Study Design	Cohort/Data Source	Follow-up (y)	Mean Age at Diagnosis of BC (y)	BC-Free When Enrolled	Mutation Type	No. of Patients Undergoing Surgery	No. of BC Cases	Adjustment Factors
Chang-Claude (2007)[26]	RCT	International *BRCA1/2* Carrier Cohort Study	NA	41.5	Both: 1601	*BRCA1*: 1187 *BRCA2*: 414	NA	NA	No. of children, HRT use
Eisen (2005)[27]	CC	48 different centers in 7 countries in North America, Europe, Israel	16.5 (mean)	*BRCA1*: 38.9 *BRCA2*: 40.9	No: 3305	*BRCA1*: 2432 *BRCA2*: 873	RRSO: 166 Non-RRSO: 3139	NA	Oral contraceptive use, parity

Abbreviations: BC = breast cancer; CC = case–control; HBOC, hereditary breast/ovarian cancer; HRT = hormone replacement therapy; MSKCC = Memorial Sloan Kettering Cancer Center; NA = not applicable; PCS, prospective cohort study; RCT = randomized controlled trial; RRM = risk-reducing mastectomy; RRSO = risk-reducing salpingo-oophorectomy; UBC, unilateral breast cancer.

RRSO and BC Risk

Fourteen studies explored the relationship between RRSO and BC risk (Table 1).[9-11,16,17,19-27] In these studies, patients in 8 studies had no history of BC before surgery[9-11,16,19-21,27] and patients from 5 studies had a history of BC.[11,17,19,24,25] Both populations were discussed in 2 studies: Domchek et al[11] and Mavaddat et al.[19] Three other studies did not distinguish whether the population had a history of BC.[22,23,26]

Eight studies showed that a population with no history of BC before RRSO was associated with a reduced risk of BC in *BRCA1/2* carriers (HR = 0.58; 95% CI, 0.37 to 0.78), but a moderate heterogeneity (I^2 = 69.2%, $P_{heterogeneity}$ = .002, n = 8) was explored.[9-11,16,19-21,27] Then we divided the data into 2 subgroups of *BRCA1* and *BRCA2* according to the different subtypes of the *BRCA* gene, and performed a subgroup analysis. We observed that there was no difference (P = .497) between people with *BRCA1* or *BRCA2* (*BRCA1*: HR = 0.65; 95% CI, 0.42 to 0.87, I^2 = 64.4%, $P_{heterogeneity}$ = .015, n = 6; *BRCA2*: HR = 0.53; 95% CI, 0.33 to 0.74, I^2 = 0.0%, $P_{heterogeneity}$ = .727, n = 5; $P_{heterogeneity}$ = .497) (Table 3).

Similar results from 5 studies indicated that RRSO could reduce BC risk (HR = 0.50; 95% CI, 0.31 to 0.69, I^2 = 4.4%, $P_{heterogeneity}$ = .382, n = 5) in *BRCA1/2* carriers with a history of BC before RRSO.[11,17,19,24,25] We also did not observe significant differences in the gene subgroup analysis (P = .848), *BRCA1* (HR = 0.51; 95% CI, 0.20 to 0.83, I^2 = 44.8%, $P_{heterogeneity}$ = .142, n = 4), and *BRCA2* (HR = 0.24; 95% CI, −0.05 to 0.52, I^2 = 0.0%, $P_{heterogeneity}$ = .586, n = 4) (Table 3).

In the process of studying the relationship between BC risk and RRSO, we found that 3 studies addressing this issue did not indicate whether the population had a history of BC before surgery.[22,23,26] We combined the results of these 3 studies and found that RRSO also can reduce BC risk in this population (HR = 0.59; 95% CI, 0.45 to 0.74), and no heterogeneity was found (I^2 = 0.0%, $P_{heterogeneity}$ = .883, n = 3). We did not analyze the genetic subgroups of this population because there were too few studies (Table 3).

In addition, 4 studies summarized the impact of age at RRSO on the risk of BC.[10,11,26,27] Although no statistically significant differences were found between age > 50 years and age < 50 years groups (P = .212), analysis of data revealed that RRSO had a trend of benefit for *BRCA* carriers who were < 50 (HR = 0.45; 95% CI, 0.24 to 0.67) (Table 3).

Finally, we conducted a subgroup analysis of related studies according to the year of publication.[9-11,16,17,19-27] We divided the studies into 3 groups (<2010; 2010-2015, >2015) and found that the earliest studies found that RRSO had protective benefits for *BRCA* carriers (For studies published before 2010, HR = 0.43; 95% CI, 0.31 to 0.54, n = 7; For studies published between 2010 and 2015, HR = 0.58; 95% CI, 0.47 to 0.69, n = 6).[11,17,19-27] However, the most recent 3 studies had opposite results (HR = 0.96; 95% CI, 0.65 to 1.26, n = 3).[9,10,16] This finding was statistically significant (P = .024) (Table 3).

Figure 2 provides a meta-analysis and Figure 3 a subgroup analysis of RRSO and BC risk in different populations.

Table 2 Characteristics of 6 Mortality-Related Studies Included in Meta-analysis

Study	Study Design	Cohort/Data Source	Mean Follow-up (y)	Mean Age at Diagnosis of BC (y)	BC-Free When Enrolled	Mutation Type	No. of Patients Undergoing Surgery	No. of All-cause Mortality Cases	Adjustment Factors
Domchek (2010)[11]	PCS	22 centers in PROSE Consortium	NA	NA	No: 1458	*BRCA1*: 935 *BRCA2*: 523	RRSO: 447 Non-RRSO: 1011	RRSO: 8 Non-RRSO: 60	Year of birth, stratified by center
					Yes: 1027	*BRCA1*: 654 *BRCA2*: 373	RRSO: 451 Non-RRSO: 576	RRSO: 19 Non-RRSO: 92	
Finch (2014)[13]	PCS	43 centers in Canada, United States, Austria, France, Italy, Norway, Poland	5.6 (mean)	NA	No: 2633	NA	RRSO: 1702 Non-RRSO: 1334	NA	Age at study entry, oral contraceptive use, parity, mutation, history of breast cancer at baseline
					Yes: 2561	NA	RRSO: 1736 Non-RRSO: 825	NA	
Evans (2013)[28]	PCS	Multicenter European collaboration	NA	RRSO: 43.89 Non-RRSO: 44.65	Yes: 593 (UBC)	NA	RRSO: 120 Non-RRSO: 473	RRSO: 15 Non-RRSO: 165	Tumor grade, stage, ER status; investigating RRSO effects
Huzarski (2016)[18]	RCT	17 affiliated clinical centers situated throughout Poland	NA	42.8	Yes: 476	*BRCA1*: 476	RRSO: 242 Non-RRSO: 229 Missing: 5	RRSO: 21 Non-RRSO: 66 Missing: 1	NA
Metcalfe (2015)[12]	RCT	12 participating clinical genetics centers	NA	RRSO: 41.7 Non-RBSO: 42.6	Yes: 676	*BRCA1*: 411 *BRCA2*: 254 *BRCA1* and 2: 11	RRSO: 345 Non-RRSO: 331	RRSO: 26 Non-RRSO: 131	Age at diagnosis, year of diagnosis, *BRCA* gene, tumor size, nodal status, estrogen receptor status, receipt of chemotherapy, tamoxifen use, oophorectomy, contralateral mastectomy, ipsilateral mastectomy
Van Sprundel (2005)[29]	RCT	Netherlands Cancer Institute, Amsterdam; Leiden University Medical Centre, Leiden	3.5 (mean)	NA	Yes: 148 (UBC)	*BRCA1*: 115 *BRCA2*: 33	NA	NA	CPM, time between first breast cancer between first breast cancer and start follow-up and chemotherapy

Abbreviations: CPM = contralateral prophylactic mastectomy; ER = estrogen receptor; NA = not applicable; PCS, prospective cohort study; RCT = randomized controlled trial; RRSO = risk-reducing salpingo-oophorectomy; UBC, unilateral breast cancer.

Table 3 Subgroup Analysis

Group	BC Risk					All-Cause Mortality				
	No. of Studies	No. of Population	HR (95% CI)	I^2 (%)	*P*	No. of Studies	No. of Population	HR (95% CI)	I^2 (%)	*P*
BC-Free										
BRCA1/2	8[e]	10,447	0.58 (0.37 to 0.78)	69.2		2	4091	0.27 (0.10 to 0.43)	17.3	
BRCA1	6	7461	0.65 (0.42 to 0.87)	64.4	.497	2	NA	0.29 (0.02 to 0.55)	40.9	.801
BRCA2	5	2817	0.53 (0.33 to 0.74)	0		1[a]	NA	0.67 (0.08 to 5.35)	—	
Previous BC										
BRCA1/2	5	2200	0.50 (0.31 to 0.69)	4.4		6	5481	0.33 (0.28 to 0.38)	0	
BRCA1	4	1215	0.51 (0.20 to 0.83)	44.8	.848	3	NA	0.31 (0.24 to 0.38)	0	.730
BRCA2	4	808	0.24 (−0.05 to 0.52)	0		3	NA	0.36 (0.22 to 0.50)	0	
Mixed[f]										
BRCA1/2	3	4560	0.59 (0.45 to 0.74)	0						
BRCA1	1[a]	368	0.61 (0.30 to 1.22)	—	—					
BRCA2	1[a]	229	0.28 (0.08 to 0.92)	—						
Age at RRSO										
<50 y	4	NA	0.45 (0.24 to 0.67)	59.8	.212	3	NA	0.30 (0.21 to 0.39)	27.7	.840
>50 y	3	NA	0.83 (0.01 to 1.66)	0		3	NA	0.32 (0.22 to 0.42)	5.2	
Sample Size										
<1000	11[b]	4847	0.51 (0.34 to 0.68)	39.7	.530	4	1893	0.37 (0.26 to 0.49)	0	.670
>1000	5	12,360	0.61 (0.46 to 0.76)	58.1		4[b]	3588	0.31 (0.25 to 0.36)	0	
Area[c]										
Europe	6[b]	4268	0.54 (0.30 to 0.79)	48.9	.422	3	1217	0.39 (0.24 to 0.55)	0	.844
American	5	4658	0.55 (0.22 to 0.87)	70.1		1[a]	676	0.35 (0.22 to 0.56)	—	
Follow-up										
<5 y	8[b]	5217	0.59 (0.39 to 0.79)	51.4	.238	2	1175	0.29 (0.13 to 0.44)	0	.945
>5 y	7	10,389	0.54 (0.38 to 0.70)	55.2		2[b]	4927	0.29 (0.21 to 0.37)	32.1	
Publication Year										
<2010	7	6143	0.43 (0.31 to 0.54)	0	.024	1	148	0.23 (0.07 to 0.78)	—	.788
<2015 and ≥2010	6	6414	0.58 (0.47 to 0.69)	0		5	8272	0.31 (0.26 to 0.37)	0	
≥2015	3	4650	0.96 (0.65 to 1.26)	16.7		2	1152	0.37 (0.24 to 051)	0	

Table 3 Continued

Group	BC Risk					All-Cause Mortality				
	No. of Studies	No. of Population	HR (95% CI)	I^2 (%)	*P*	No. of Studies	No. of Population	HR (95% CI)	I^2 (%)	*P*
Surgical Type										
Mixed[d]	8[b]	7042	0.57 (0.37 to 0.77)	54.6	.238	3[b]	2961	0.35 (0.23 to 0.48)	0	.807
Bilateral	8[b]	10,165	0.56 (0.41 to 0.70)	43.5		5[b]	6611	0.31 (0.26 to 0.37)	0	

Abbreviations: BC = breast cancer; CI = confidence interval; HR = hazard ratio; RRSO = risk-reducing salpingo-oophorectomy.
[a]Because there was only one relevant study included, corresponding data in original study were directly cited.
[b]In publication, researchers observed first incidence of BC in women without history of BC and recurrence of BC in women with history of BC. At this time, they would be regarded as 2 studies.
[c]We only included population from Europe or Americas, excluded population from both Americas and Europe, or other regions.
[d]Study did not explicitly mention whether RRSO was bilateral or unilateral.
[e]Data were that of all study members included in this group.
[f]Population in this part of study did not explain whether there was history of BC before RRSO.

RRSO and Survival

A total of 6 studies investigated the relationship between RRSO and all-cause mortality of BC (Table 2).[11-13,18,28,29] Two of the studies involved populations with no history of BC before surgery.[11,13] Six studies had a population with a history of BC.[11-13,18,28,29] The studies of Domchek et al[11] and Finch et al[13] discussed both populations. Among these 6 studies, 4 also conducted a further study on the BC-specific mortality.[11,12,18,29]

After we analyzed 2 studies, we concluded that RRSO can reduce all-cause mortality (HR = 0.27; 95% CI, 0.10 to 0.43) of *BRCA1/2* carriers in people without a history of BC before surgery, without heterogeneity ($I^2 = 17.3\%$, $P_{heterogeneity} = .272$, n = 2).[11,13] We also analyzed different gene subtypes, and we observed that RRSO can also reduce the all-cause mortality of *BRCA1* carriers (HR = 0.29; 95% CI, 0.02 to 0.55, $I^2 = 40.9\%$, $P_{heterogeneity} = .193$, n = 2), although there was no statistical difference for *BRCA2* ($P = .801$) (Table 3).

From the related 6 studies, we obtained the same conclusion in people with *BRCA1/2* who had a history of BC before surgery (HR = 0.33; 95% CI, 0.28 to 0.38), without heterogeneity ($I^2 = 0.0\%$, $P_{heterogeneity} = .843$, n = 6).[11-13,18,28,29] There was also no obvious statistical difference between *BRCA1* (HR = 0.31; 95% CI, 0.24 to 0.38, $I^2 = 0$, $P_{heterogeneity} = .790$, n = 3) and *BRCA2* (HR = 0.36; 95% CI, 0.22 to 0.50, $I^2 = 0$, $P_{heterogeneity} = .717$, n = 3) (Table 3).

Four studies explored the effect of RRSO on BC-specific mortality.[11,12,18,29] Our statistical analysis revealed that RRSO can reduce BC-specific mortality in people with a history of BC before surgery (HR = 0.42; 95% CI, 0.27 to 0.58, $I^2 = 0.0\%$, $P_{heterogeneity} = .659$, n = 4).

We then investigated 3 studies that mentioned the relationship between age at all-cause mortality and RRSO in *BRCA1/2* carriers, regardless of history of BC.[11-13] Statistical analysis revealed no significant difference ($P = .840$) for people who died after RRSO at age < 50 years (HR = 0.30; 95% CI, 0.21 to 0.39, $I^2 = 27.7\%$, $P_{heterogeneity} = .246$, n = 3) or age > 50 years (HR = 0.32; 95% CI, 0.22 to 0.42, $I^2 = 5.2\%$, $P_{heterogeneity} = .367$, n = 3) (Table 3).

Figure 4 provides a meta-analysis and Figure 5 a subgroup analysis of RRSO and survival in different populations.

Other Subgroup Analysis

We also conducted statistical analysis of the follow-up time, sample size, geographic area, and surgical approach of each study, but no statistically significant differences were found (Table 3).

Publication Bias

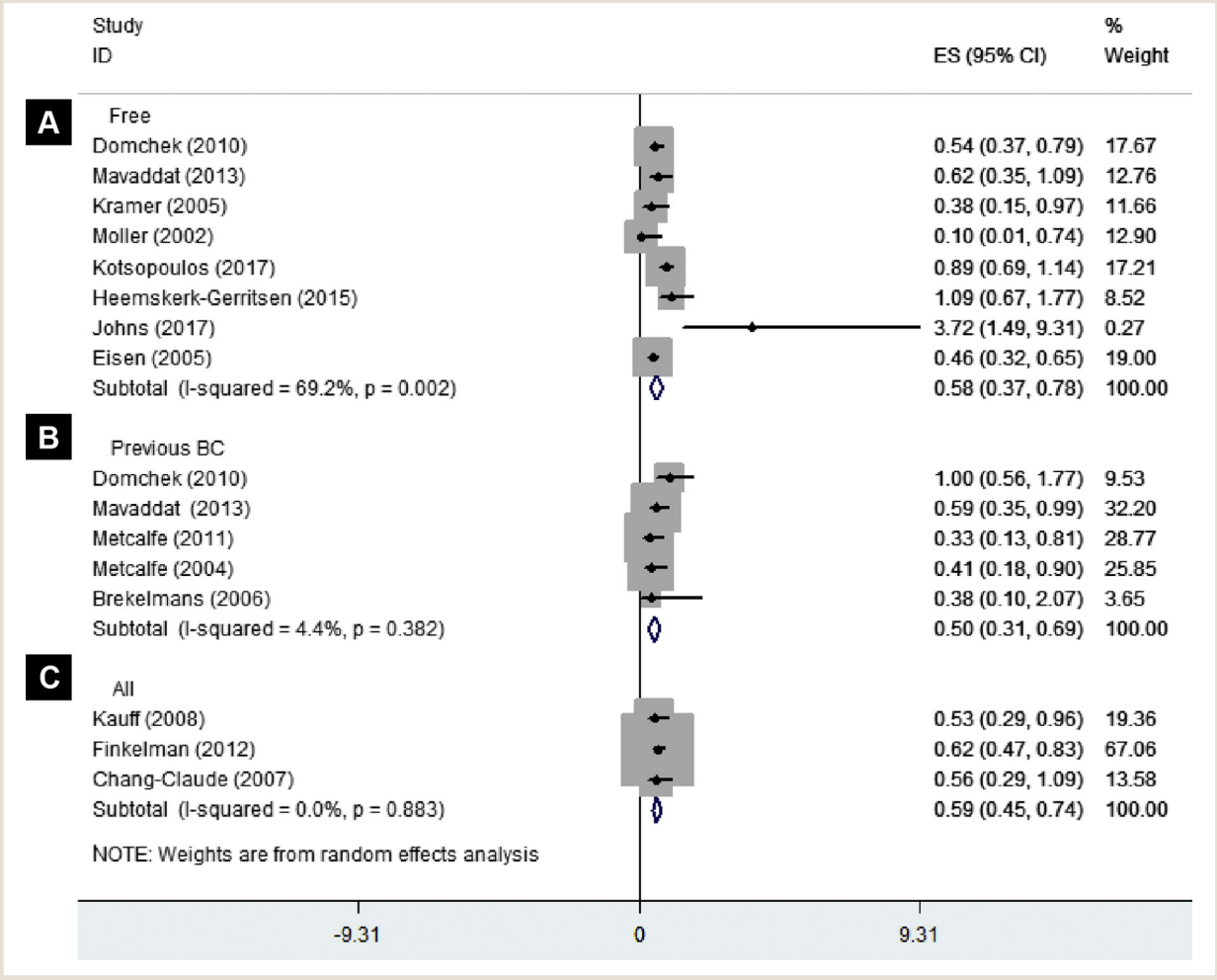
We found no evidence of publication bias in any analyses using the Begg or Egger tests (all $P > .05$).

Discussion

To our knowledge, this is the most comprehensive and largest study to systematically investigate RRSO in *BRCA1/2* mutation carriers with BC. We have summarized the evidence for RRSO in BC risk and mortality in women with *BRCA1/2* mutations.

In our study, RRSO was associated with a 42% lower risk of BC in women with *BRCA1/2* mutations and no history of BC. Although there was no statistically significant difference between the 2 subgroups, the postoperative effect of the *BRCA1* mutation on

Figure 2 Meta-analysis of RRSO and BC Risk in Different Populations. Patients With (A) No History or (B) History of BC Before RRSO. (C) Three Studies Did Not Indicate Whether There Was History of BC Before RRSO



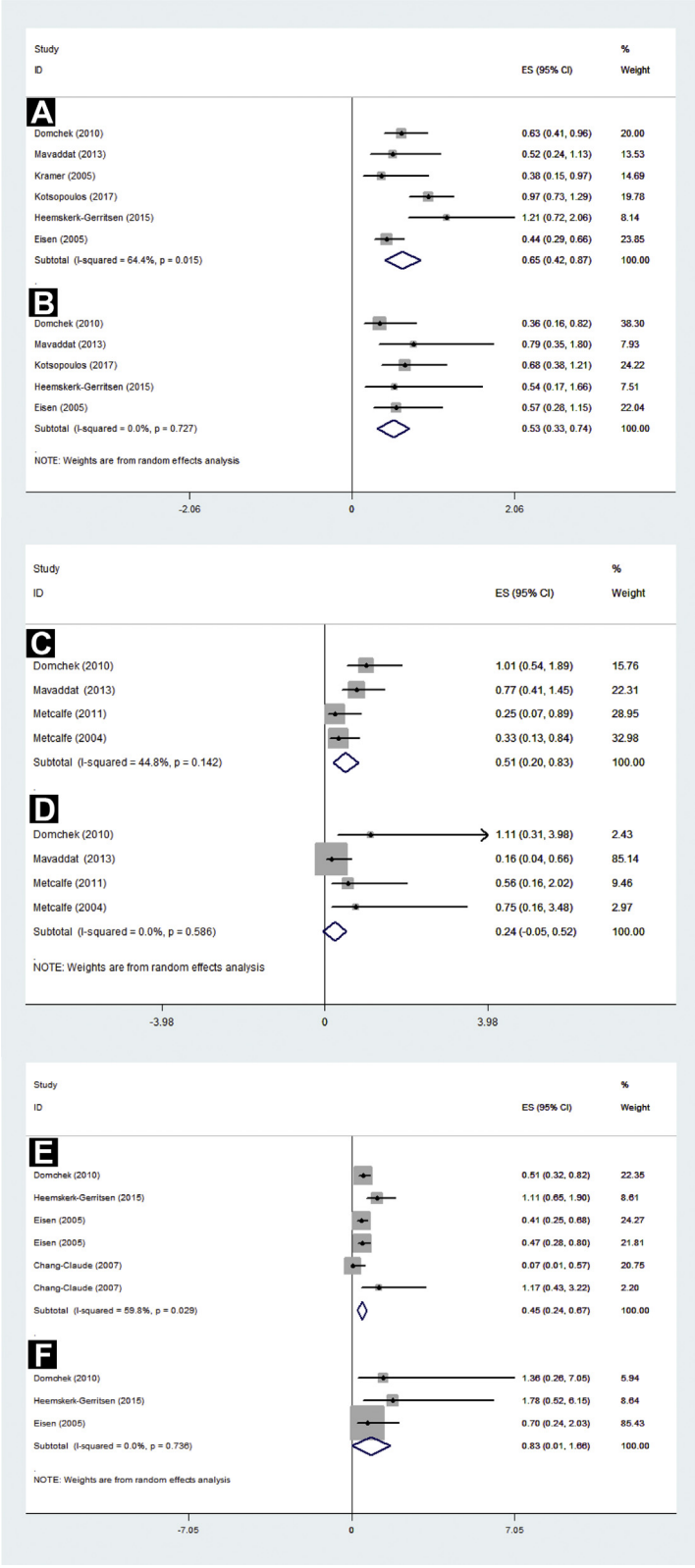
Abbreviations: BC = breast cancer; RRSO = risk-reducing salpingo-oophorectomy.

women was superior to that of women with the *BRCA2* mutation. RRSO also had a protective effect on women with preoperative BC, reducing the risk of recurrence by about 50%.

Most of the early studies found that RRSO could reduce the incidence of BC.[11,17,19-21,27] A study by Domchek et al[11] mentioned that RRSO was associated with a reduced risk of BC in women with no history of BC, and there were no significant differences between *BRCA1* and *BRCA2* mutation carriers. In addition, Li et al[7] found that in *BRCA1* mutation carriers with no history of BC, RRSO had an age-related risk of reducing BC risk before the age of 50, but no protective effect after the age of 50. More recent studies, however, do not have results consistent with this.[9,10,16] The study of Kotsopoulos et al[9] was the largest prospective analysis of BC risk after RRSO in women with *BRCA1* or *BRCA2* mutations. During follow-up, 350 of 3722 women with undiagnosed *BRCA1/2* mutation ended up with BC, with an average follow-up time of 5.6 years. Finally, they found no statistically significant association between RRSO and BC risk, whether they had *BRCA1* or *BRCA2* mutations (after adjusting for age). However, they added in their stratified analysis that RRSO only reduces the risk of BC in *BRCA2* mutation carriers younger than 50 years of age (after adjusting for age). Similarly, in a retrospective study by Heemskerk-Gerritsen et al,[10] 89 cases of BC were ultimately found in 822 women with no history of BC, with a median follow-up of 3.2 years; nor was there a statistically significant association between RRSO and BC risk.

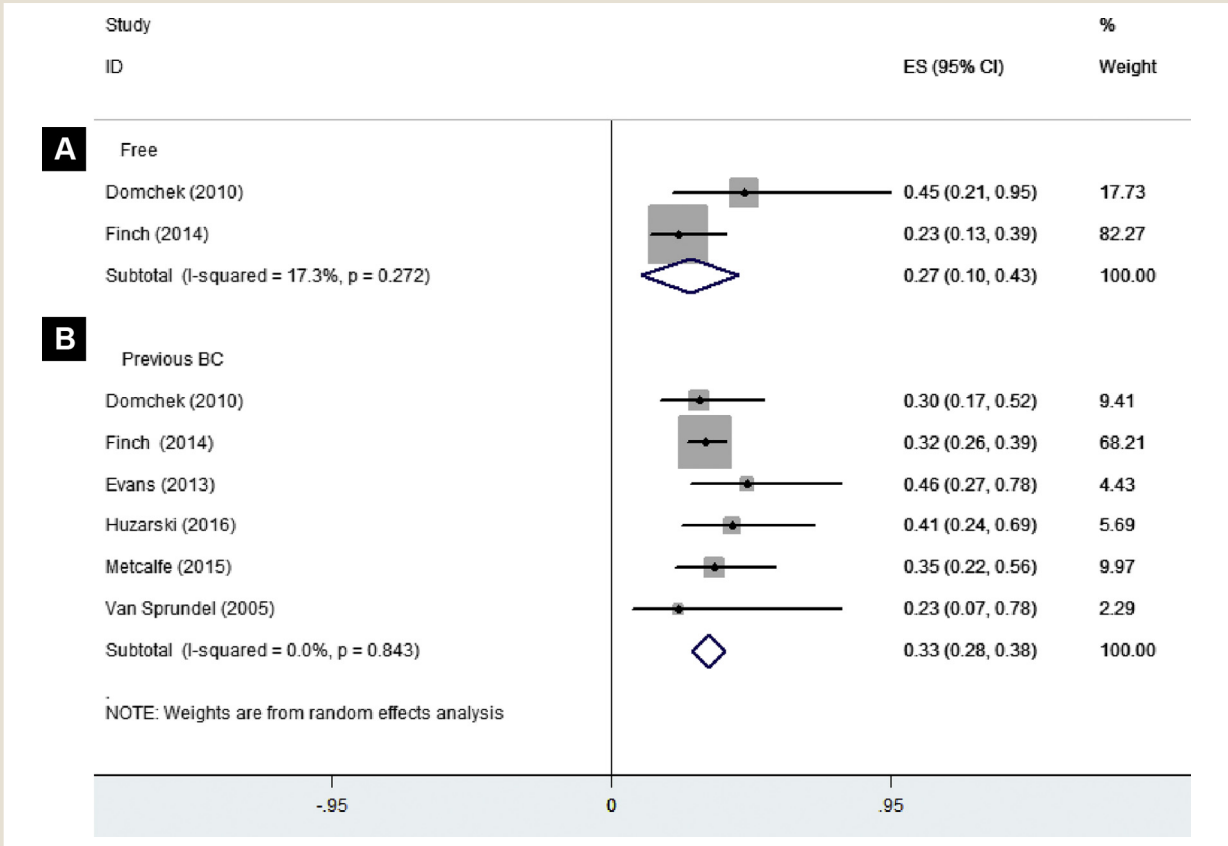
Other than that, we found that in women without a history of BC, RRSO could reduce all-cause mortality by approximately 73%. Further, the risk of *BRCA1* carriers was significantly reduced, although insufficient data regarding *BRCA2* meant valid results could not be obtained. For women who had preoperative BC, the postoperative all-cause mortality rate was lower than that of women without a history of BC, which was a decrease of 67%. There were no statistically significant differences between the 2 subgroups (*BRCA1* 69% and *BRCA2* 64%) ($P = .730$). Finally, we concluded that RRSO could reduce the all-cause mortality rate before or after

Figure 3 Subgroup Analysis of RRSO and BC Risk. Subgroup Analyses of (A) RRSO and (B) BC in Patients Without History of BC. Analyses of (C) RRSO and (D) BC Risk in Patients With History of BC. Subgroup Analyses of (E) Age at RRSO and (F) BC Risk



Abbreviations: BC = breast cancer; RRSO = risk-reducing salpingo-oophorectomy.

Figure 4 Meta-analysis of RRSO and Survival in Different Populations. (A) Patients in 2 Studies Had No History of BC Before RRSO. (B) Patients in 6 Studies Had History of BC Before RRSO



Abbreviations: BC = breast cancer; RRSO = risk-reducing salpingo-oophorectomy.

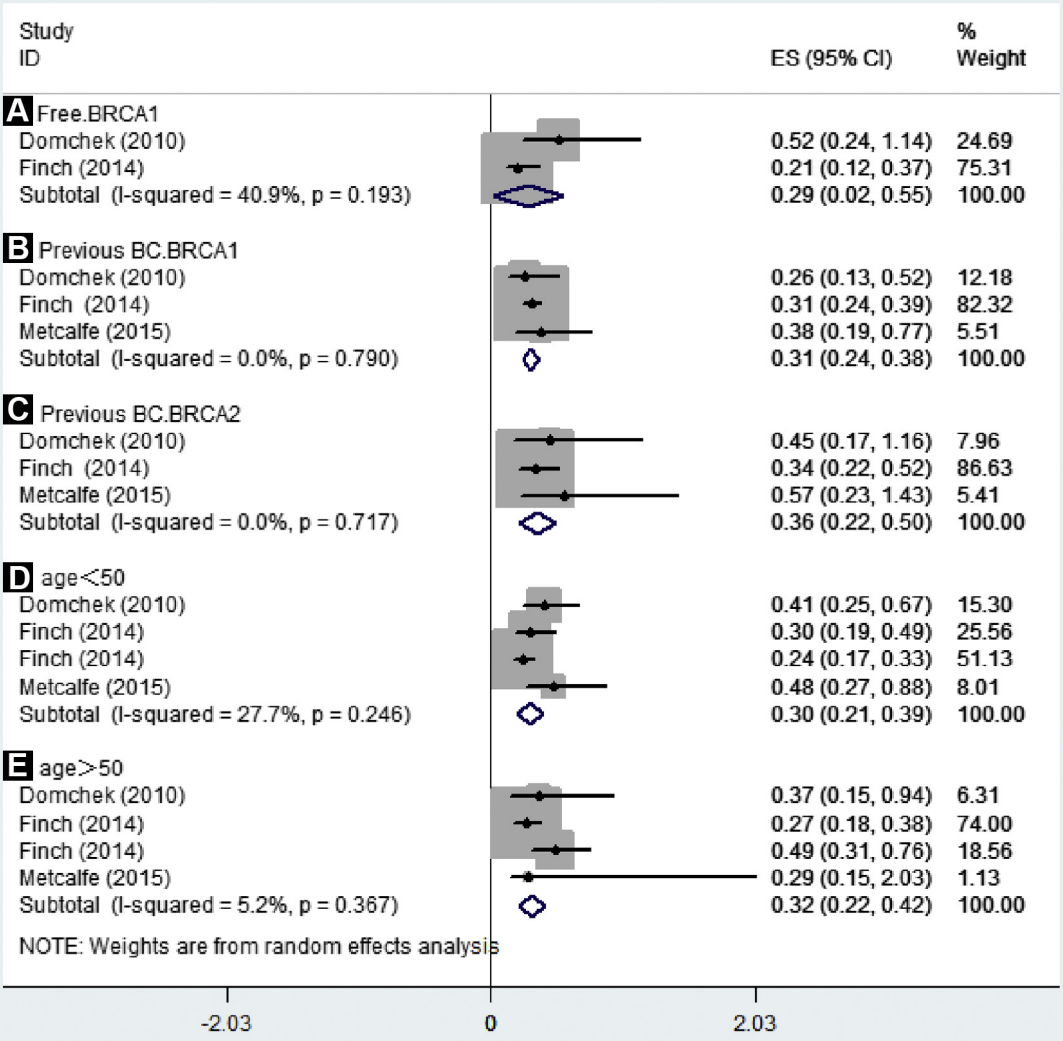
the age of 50 ($P = .840$) after analyzing the statistics of 3 related studies.[11-13]

Many studies reported that RRSO can reduce patient mortality. In the study of Finch et al,[13] with an average follow-up of 5.6 years, with 68 deaths in 5783 subjects, RRSO had reduced all-cause mortality for 77% of women with no history of BC who were under the age of 70, and they had a 68% reduction with a history of BC. Domchek et al[11] reached similar conclusions, but they also further explored the relationship between overall survival rate and RRSO performed on subjects at different ages. They found no overall difference in all-cause mortality between groups under age 50 and those over 50. However, Metcalfe et al[12] suggested that people over 50 could not benefit from RRSO. They also stratified *BRCA* gene according to mutations types, and concluded that RRSO did not reduce the all-cause mortality of *BRCA2* carriers with a history of BC. Domchek et al[11] not only drew the same conclusion but also found that RRSO did not reduce the BC-specific mortality rate of BC in *BRCA2* carriers.

There are several reasons for these differences. In the studies we included, Kotsopoulos et al[9] and Heemskerk-Gerritsen et al[10] suggested that RRSO does not reduce BC risk, contrary to the findings of many earlier studies. We observed that the population included in Kotsopoulos et al[9] were all *BRCA1/2* mutation carriers who did not have a history of BC, whereas in the early part of the study women in the cohort had mixed BC history. First of all, the risk of recurrence in this subset of women was higher than that of women who had never had BC. Second, women with a history of BC were more likely to choose preventive surgical treatment than women without BC. Therefore, in the study involving women with a history of BC, the incidence of BC (ipsilateral recurrence and contralateral occurrence) and the surgical rate of RRSO were higher, so there was a certain bias. In addition, the study by Kotsopoulos et al[9] was the largest study (n = 3722) with regard to the direction of this research, and the number of final events was the highest in the same study so far (n = 350). Early studies of the same kind were subject to many limitations, with small sample sizes and short follow-up times. Therefore, there was bound to be an error compared to the study by Kotsopoulos et al.

Further, Heemskerk-Gerritsen et al[10] noted that RRSO resulting in a decreased BC risk in *BRCA1/2* mutant carriers in the prior study could be caused by some bias. They found that some women had a history of undergoing risk-reducing mastectomy (RRM) before RRSO in some of the earlier studies, which caused a certain bias. On the one hand, the implementation of RRM had caused a difference on the observation time of the RRSO and non-RRSO groups; in particular, the observation time of non-RRSO was

Figure 5 Subgroup Analysis of RRSO and Survival. (A) Subgroup Analyses in RRSO and Survival in Patients Without History of BC. Subgroup Analyses of (B) RRSO and (C) Survival in Patients Without History of BC. Subgroup Analyses of (D) RRSO and (E) Age at All-cause Mortality



Abbreviations: BC = breast cancer; RRSO = risk-reducing salpingo-oophorectomy.

greatly reduced. On the other hand, the majority of women in the non-RRSO group were young; they had not yet had children, and/or they had not reached the age at which RRSO is recommended by the Netherlands (35-40 years old for *BRCA1* mutation carriers and 40-45 years old for *BRCA2* mutation carriers). Therefore, this population of young women may prefer RRM, which differs from the group without RRSO or RRM. Interestingly, we divided the related studies into 3 subgroups according to the study's publication year, and corresponding subgroup analyses in BC risk ($P_{heterogeneity}$ = .024) indicated that publication year was a critical interaction factor. A significant time trend in decreased BC prevention benefits of RRSO for patients with *BRCA1/2* mutation may be due to increases in hormone replacement therapies.

We also observed differences in the incidence and survival of BC with different *BRCA* subtype mutations. Mavaddat et al[30] had suggested that this problem might be explained by the pathology and etiology of *BRCA1/2*-related BC. Earlier studies had reported that estrogen receptor (ER) and progesterone receptor were mostly negative in *BRCA1* mutation carriers, while ER and progesterone receptor in *BRCA2* mutation-related tumors tended to be positive, and may be more sensitive to hormone stimulation.[30,31] Kotsopoulos et al[9] conducted a statistical analysis of hormone receptor for

77% of the population and found that the ratio of *BRCA1* carriers to ER-positive BC was 27%, while that of *BRCA2* carriers was up to 80%. Finally, they concluded that RRSO had a strong protective effect on premenopausal/ER-positive BC in women with *BRCA2* mutation. From a biological point of view, this may be due to differences in endogenous levels of estrogen and progesterone caused by RRSO, which reduces the occurrence of hormone-related tumors.

Some reports highlighted the importance of RRSO at an optimal age, and suggested that RRSO was associated with increased mortality in women over 45 years of age, especially if no sequential hormone therapy was provided.[32,33] In fact, this point may be related to the age at which the annual rate of ovarian cancer begins to rise.[13] Although the ages of the different research stratification groupings were slightly different, the trend was consistent. The Women's Health Initiative in postmenopausal women does not show cardiovascular benefits from hormone therapy after RRSO, but young women may benefit from natural menopause.[34,35] Rebbeck et al[8] surveyed 462 patients and reported that hormone therapy after RRSO did not increase the risk of BC. Eisen et al[27] provided hormone therapy to women who had received RRSO and did not observe an increased risk associated with hormone therapy. However, a longer-term study is required on this important issue.

The present study had several limitations. First, few studies exist on RRSO and the incidence and survival of BC. In our study of 19 articles, after removing 9 prospective cohort studies, there were only 9 retrospective cohort studies and 1 case–control study, which made ORs and relative risks difficult to analyze. Even though the incidence of BC in *BRCA1/2* carriers was less than 2% to 4%, we consider it to be the same as the HRs, but it still had a margin of error. Second, we tried to extract the HRs from studies as associated factors in the statistical process to ensure relative reliability. However, as a result of different adjustments for potential confounding variables adopted in different studies, the inconsistency of such adjustments further limit the comparability of the studies and may lead to different degrees of confusion. Third, we retained only the 19 best studies left after screening the sources of the study population, but there were still a few unavoidable overlaps in the individual study populations. For example, the PROSE database and the HEBOH database had several identical data sources; and the PROSE database incorporated new data sources (institutions) continuously over time, which resulted in statistically inaccurate results. Fourth, in most of the research we incorporated, there was uneven sampling of *BRCA1* and *BRCA2* gene mutation carriers, and a small sample size of *BRCA2* carriers in some studies led to unreliable results. Fifth, in the early days, the range of surgical resections and detailed pathologic evaluations recommended by various institutions were not uniform, which results in certain differences between studies in the same field and in different periods. That may lead to statistical errors. Sixth, there was a certain distance between the sample size of the included study (minimum of only 98) and follow-up time (2.6-16.5 years). The insufficient follow-up time made it impossible to observe the benefits of RRSO on the survival of patients. Even if we detected differences in the results of the analysis, the lack of follow-up time may still be statistically ineffective. Therefore, in order to obtain more real-world data, it is better to obtain a larger sample size and a longer follow-up. Finally, in the population included in the original studies, there was a potential selection bias between patients receiving and not receiving RRSO, which may affect the conclusions. However, because we had limited access to the initial data, we could not assess the baseline characteristics of both groups. Generally speaking, although a meta-analysis cannot completely avoid some of the shortcomings of the original study, it may still be used to arrive at more reliable conclusions than can be drawn by a single study.

Conclusion

On the basis of the summary of existing studies, we conclude that RRSO is strongly associated with a reduced risk of BC, and publication year was a critical interaction factor. In addition, RRSO can also reduce the mortality of BC patients with *BRCA* mutations to some extent. We still need more high-quality studies in future research. Large sample size, long follow-up, and clear basic information were obtained to perform an adequate meta-analysis of risk and mortality.

Clinical Practice Points

- Disagreements exist between RRSO and BC incidence and mortality.
- RRSO was associated with a significant reduction in the incidence of BC in women with BRCA1/2 mutations, regardless of history of BC. In addition, we found that RRSO could improve the survival of women with BC.
- Continuing efforts to identify a promising subset of women with *BRCA1/2* mutations receiving RRSO should be made in further clinical trials.

Disclosure

The authors have stated that they have no conflict of interest.

Supplemental Data

Supplemental tables accompanying this article can be found in the online version at https://doi.org/10.1016/j.clbc.2018.09.011.

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Supplemental Table 1 Search History of PubMed Search Strategy

No.	Search Strategy	No. of Items
1	(*BRCA1*[MeSH]) OR *BRCA2*[MeSH]	5755
2	(*BRCA1*[Title/Abstract]) OR *BRCA1* mutation[Title/Abstract]	11,844
3	(*BRCA2*[Title/Abstract]) OR *BRCA2* mutation[Title/Abstract]	6517
4	#1 OR #2 OR #3	14,874
5	oophorectomy[MeSH]	23,260
6	(oophorectomy[Title/Abstract]) OR salpingo-oophorectomy[Title/Abstract]	7901
7	#5 OR #6	28,390
8	breast cancer[MeSH]	253,3955
9	(breast[Title/Abstract]) OR mammary[Title/Abstract]	409,413
10	(((cancer[Title/Abstract]) OR neoplasm[Title/Abstract]) OR tumors[Title/Abstract]) OR malignancy[Title/Abstract]	1,819,749
11	#9 AND #10	281,391
12	#8 OR #11	348,916
13	#4 AND #7 AND #12	580

PubMed search strategy with superior search capabilities was adapted for use with other databases. Items were found in Embase database (n = 513) until November 26, 2017.

Supplemental Table 2 Reasons for Exclusion of Full Manuscripts Screened but Not Included in Meta-analysis

No.	Title	Year	Reason[a]
01	High demoralization in a minority of oophorectomized *BRCA1/2* mutation carriers influences quality of life	2017	1
02	The effect of hormone therapy on quality of life and breast cancer risk after risk-reducing salpingo-oophorectomy: a systematic review	2017	2
03	Risk of contralateral breast cancer in *BRCA1* and *BRCA2* mutation carriers: a 30-year semi-prospective analysis	2017	4
04	Risk reduction strategies in breast cancer prevention	2017	2
05	Mortality reduction and cost-effectiveness of performing hysterectomy at the time of risk-reducing salpingo-oophorectomy for prophylaxis against serous/serous-like uterine cancers in *BRCA1* mutation carriers	2017	1
06	Pathologic findings at risk-reducing salpingo-oophorectomy (RRSO) in germline *BRCA* mutation carriers with breast cancer: significance of bilateral RRSO at the optimal age in germline *BRCA* mutation carriers	2017	8
07	The role of risk-reducing surgery in hereditary breast and ovarian cancer	2016	2
08	Effectiveness of prophylactic surgeries in *BRCA1* or *BRCA2* mutation carriers: a meta-analysis and systematic review	2016	5
09	Occult and subsequent cancer incidence following risk-reducing surgery in *BRCA* mutation carriers	2016	1
10	Uptake of risk-reducing salpingo-oophorectomy among female *BRCA* mutation carriers: experience at the National Cancer Center of Korea	2016	1
11	Risk reduction and survival benefit of prophylactic surgery in *BRCA* mutation carriers: a systematic review	2016	2
12	Risk assessment, genetic counseling, and genetic testing for *BRCA*-related cancer in women: a systematic review to update the US Preventive Services Task Force Recommendation	2014	2
13	Contralateral mastectomy and survival after breast cancer in carriers of *BRCA1* and *BRCA2* mutations: retrospective analysis	2014	4
14	Surgical management of breast cancer in *BRCA*-mutation carriers: a systematic review and meta-analysis	2014	5
15	Survival patterns after oophorectomy in premenopausal women: a population-based cohort study	2014	10
16	Preventing breast and ovarian cancers in high-risk *BRCA1* and *BRCA2* mutation carriers	2013	1
17	Substantial breast cancer risk reduction and potential survival benefit after bilateral mastectomy when compared to surveillance in healthy *BRCA1* and *BRCA2* mutation carriers: a prospective analysis	2013	1
18	The impact of prophylactic salpingo-oophorectomy on quality of life and psychological distress in women with a *BRCA* mutation	2013	1
19	Long term follow up of *BRCA1* and *BRCA2* mutation carriers with unsuspected neoplasia identified at risk reducing salpingo-oophorectomy	2013	1
20	Ten-year survival in patients with *BRCA1*-negative and *BRCA1*-positive breast cancer	2013	4
21	Risk-reducing surgery increases survival in *BRCA1/2* mutation carriers unaffected at time of family referral	2013	4
22	Breast cancer incidence after risk-reducing salpingo-oophorectomy in *BRCA1* and *BRCA2* mutation carriers	2012	8
23	*BRCA* carriers, prophylactic salpingo-oophorectomy and menopause: clinical management considerations and recommendations	2012	2
24	Long-term outcomes of *BRCA1/BRCA2* testing: risk reduction and surveillance	2012	1
25	Effectiveness of risk-reducing salpingo-oophorectomy in preventing ovarian cancer in a high-risk French Canadian population	2012	1
26	Breast and ovarian cancer risk management in a French cohort of 158 women carrying a *BRCA1* or *BRCA2* germline mutation: patient choices and outcome	2012	1
27	The impact of prophylactic salpingo-oophorectomy on menopausal symptoms and sexual function in women who carry a *BRCA* mutation	2011	1
28	Surgical management of an Irish cohort of *BRCA*-mutation carriers	2011	1
29	Breast cancer after bilateral risk-reducing mastectomy	2011	1
30	Risk-reducing salpingo-oophorectomy in *BRCA1* and *BRCA2* mutation carriers	2011	1
31	Breast cancer screening in *BRCA1* and *BRCA2* mutation carriers after risk reducing salpingo-oophorectomy	2011	1
32	Populační studie rizika druhého primárního kontralaterálního karcinomu prsu spojeného s nosičstvím mutace v *BRCA1* nebo *BRCA2*	2010	9
33	Risk-reducing strategies for women carrying *BRCA1/2* mutations with a focus on prophylactic surgery	2010	1
34	Survival analysis of cancer risk reduction strategies for *BRCA1/2* mutation carriers	2010	2
35	Contralateral risk-reducing mastectomy in *BRCA1* and *BRCA2* mutation carriers and other high-risk women in the Kathleen Cuningham Foundation Consortium for Research into Familial Breast Cancer (kConFab)	2010	10
36	Prophylactic and risk-reducing bilateral salpingo-oophorectomy: recommendations based on risk of ovarian cancer	2010	6
37	Risk-reducing surgery for ovarian cancer: outcomes in 300 surgeries suggest a low peritoneal primary risk	2009	1

Supplemental Table 2 Continued

No.	Title	Year	Reason[a]
38	Breast and ovarian cancer risk perception after prophylactic salpingo-oophorectomy due to an inherited mutation in the *BRCA1* or *BRCA2* gene	2009	1
39	Oophorectomy for breast cancer prevention in women with *BRCA1* or *BRCA2* mutations	2009	2
40	Meta-analysis of risk reduction estimates associated with risk-reducing salpingo-oophorectomy in *BRCA1* or *BRCA2* mutation carriers	2009	5
41	What have we learned from risk-reducing salpingo-oophorectomy?	2009	2
42	Uptake, time course, and predictors of risk-reducing surgeries in *BRCA* carriers	2009	1
43	Prophylactic oophorectomy in women at increased cancer risk	2007	2
44	Effectiveness of preventive interventions in *BRCA1/2* gene mutation carriers: a systematic review	2007	2
45	The prevention of hereditary breast cancer	2007	2
46	Tumour characteristics, survival and prognostic factors of hereditary breast cancer from *BRCA2*-, *BRCA1*- and non-*BRCA1/2* families as compared to sporadic breast cancer cases	2007	3
47	Prophylactic bilateral salpingo- oophorectomy compared to surveillance in women with *BRCA* mutations	2006	1
48	Mortality after bilateral salpingo-oophorectomy in *BRCA1* and *BRCA2* mutation carriers: a prospective cohort study	2006	4
49	Salpingo-oophorectomy and the risk of ovarian, fallopian tube, and peritoneal cancers in women with a *BRCA1* or *BRCA2* mutation	2006	7
50	The significance of cytologic mesothelial atypia diagnosed from peritoneal washings performed during risk-reducing salpingo-oophorectomy	2006	1
51	Can bilateral prophylactic salpingo-oophorectomy reduce cancer mortality in carriers of a *BRCA1* or *BRCA2* mutation?	2006	2
52	Outcome of surveillance and prophylactic salpingo-oophorectomy in asymptomatic women at high risk for ovarian cancer	2005	1
53	Effect of short-term hormone replacement therapy on breast cancer risk reduction after bilateral prophylactic oophorectomy in *BRCA1* and *BRCA2* mutation carriers: the PROSE study group	2005	4
54	Bilateral oophorectomy and breast cancer risk reduction among women with a family history	2004	8
55	Efficacy of Risk-reducing salpingo-oophorectomy in women with *BRCA-1* and *BRCA-2* mutations	2004	2
56	Clinical outcome of prophylactic oophorectomy in *BRCA1/BRCA2* mutation carriers and events during follow-up	2004	1
57	Surgical risk reduction: prophylactic salpingo-oophorectomy and prophylactic mastectomy	2004	1
58	Prophylactic oophorectomy to reduce the risk of ovarian and breast cancer in carriers of *BRCA* mutations	2002	6
59	Prophylactic oophorectomy in carriers of *BRCA1* or *BRCA2* mutations	2002	4
60	Risk-reducing salpingo-oophorectomy in women with a *BRCA1* or *BRCA2* mutation	2002	4
61	Prophylactic oophorectomy in *BRCA1* and *BRCA2* mutation carriers	2002	1
62	Decision analysis of prophylactic surgery or screening for mutation carriers: a more prominent role for oophorectomy	2002	2
63	Efficacy of bilateral prophylactic mastectomy in *BRCA1* and *BRCA2* gene mutation carriers	2001	1
64	Breast cancer risk after bilateral prophylactic oophorectomy in *BRCA1* mutation carriers	1999	4
65	Risk of breast cancer in carriers of *BRCA* gene mutations	1997	1

[a]Reasons for exclusion were classified as follows: 1 = no report of adjusted odds ratio, relative risk, or hazard ratio (n = 28); 2 = review (n = 15); 3 = hazard ratio includes non-*BRCA* (n = 1); 4 = duplicate studies on same study population without valid data on their contribution (n = 9); 5 = meta-analysis (n = 3); 6 = editorial (n = 2); 7 = have no relationship with breast cancer (n = 1); 8 = no control group (n = 3); 9 = article not in English (n = 1); 10 = lack of target gene carriers (n = 2).

Supplemental Table 3 Results of Quality Assessment for 17 Unique Studies Based on Newcastle-Ottawa Quality Assessment Scale

Reference	Selection[a]				Comparability[b]		Outcome[c]			Total Score[d]
	Representativeness of Exposed Cohort[e]	Selection of Nonexposed Cohort[f]	Exposure Ascertainment[g]	No Cases When Investigations Begin	Comparable on Confounder[h]		Outcome Assessment[i]	Adequate Follow-up (≥5 y)	Loss to Follow-up Rate ≤20%	
Domchek (2010)[11]	*	*	*	*	*	*	*	*	*	9
Mavaddat (2013)[19]	*	*	*	*	*	*	*		*	8
Kramer (2005)[20]	*	*	*	*	*		*	*	*	8
Finch (2014)[13]	*	*	*	*	*	*	*	*		8
Evans (2013)[28]	*	*	*	*	*		*	*	*	8
Moller (2002)[21]	*	*	*	*			*		*	6
Kauff (2008)[22]	*	*	*		*	*			*	6
Kotsopoulos (2017)[9]	*	*	*	*	*	*	*	*		8
Finkelman (2012)[23]	*	*	*		*	*		*	*	7
Heemskerk-Gerritsen (2105)[10]	*	*	*	*	*	*			*	7
Huzarski (2016)[18]	*	*	*	*	*		*	*		7
Metcalfe (2015)[12]	*	*	*	*	*	*	*	*	*	9
Metcalfe (2011)[17]	*	*	*		*	*	*	*	*	8
Metcalfe (2004)[24]	*	*	*		*	*	*	*	*	8
Van Sprundel (2005)[29]	*	*	*	*	*		*		*	7
Brekelmans (2006)[25]	*	*	*		*		*	*	*	7
Johnse (2017)[16]	*	*	*	*	*		*		*	7
Chang-Claude (2007)[26]		*	*	*	*		*		*	6
Eisen (2005)[27]	*	*	*	*	*	*	*		*	8

[a]"Selection" part includes representativeness of cases, selection of controls, exposure ascertainment, and no breast cancer incident when investigation began.
[b]"Comparability" part includes comparable on confounders.
[c]"Outcome" part includes outcome assessment, adequate follow-up, and loss to follow-up rate.
[d]Total score is equal to total number of stars.
[e]Exposed cohorts are population based or hospital based, which can award star. Population coming from nurses, volunteers, or unknown sources cannot receive star.
[f]Only same source with exposed cohorts; nonexposed cohorts are considered as selected.
[g]When exposure variables should be ascertained by medical records or questionnaires, star should be awarded.
[h]If exposed and nonexposed cohorts are based on most important factors, star is awarded. If studies adjusted for 2 individual factors among age, menopausal age, or family history of breast cancer, it is awarded another star.
[i]When breast cancer cases were identified by cancer registry, pathologic proving, or medical records, star should be awarded.