Meta-analysis of Risk Reduction Estimates Associated With Risk-Reducing Salpingo-oophorectomy in *BRCA1* or *BRCA2* Mutation Carriers

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Background Risk-reducing salpingo-oophorectomy (RRSO) is widely used by carriers of *BRCA1* or *BRCA2* (*BRCA1/2*) mutations to reduce their risks of breast and ovarian cancer. To guide women and their clinicians in optimizing cancer prevention strategies, we summarized the magnitude of the risk reductions in women with *BRCA1/2* mutations who have undergone RRSO compared with those who have not.

Methods All reports of RRSO and breast and/or ovarian or fallopian tube cancer in *BRCA1/2* mutation carriers published between 1999 and 2007 were obtained from a PubMed search. Hazard ratio (HR) estimates were identified directly from the original articles. Pooled results were computed from nonoverlapping studies by fixed-effects meta-analysis.

Results Ten studies investigated breast or gynecologic cancer outcomes in *BRCA1/2* mutation carriers who had undergone RRSO. Breast cancer outcomes were investigated in three nonoverlapping studies of *BRCA1/2* mutation carriers, four of *BRCA1* mutation carriers, and three of *BRCA2* mutation carriers. Gynecologic cancer outcomes were investigated in three nonoverlapping studies of *BRCA1/2* mutation carriers and one of *BRCA1* mutation carriers. RRSO was associated with a statistically significant reduction in risk of breast cancer in *BRCA1/2* mutation carriers (HR = 0.49; 95% confidence interval [CI] = 0.37 to 0.65). Similar risk reductions were observed in *BRCA1* mutation carriers (HR = 0.47; 95% CI = 0.35 to 0.64) and in *BRCA2* mutation carriers (HR = 0.47; 95% CI = 0.26 to 0.84). RRSO was also associated with a statistically significant reduction in the risk of *BRCA1/2*-associated ovarian or fallopian tube cancer (HR = 0.21; 95% CI = 0.12 to 0.39). Data were insufficient to obtain separate estimates for ovarian or fallopian tube cancer risk reduction with RRSO in *BRCA1* or *BRCA2* mutation carriers.

Conclusion The summary estimates presented here indicate that RRSO is strongly associated with reductions in the risk of breast, ovarian, and fallopian tube cancers and should provide guidance to women in planning cancer risk reduction strategies.

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Women who have inherited mutations in the *BRCA1* or *BRCA2* (*BRCA1/2*) genes have substantially elevated risks of breast and ovarian cancer, with a lifetime risk of breast cancer of 56%–84% (1–4). Breast cancer in *BRCA1/2* mutation carriers also occurs at an earlier age, particularly among *BRCA1* mutation carriers, than for noncarriers. The risk for ovarian cancer is dependent on whether the mutation has occurred in *BRCA1* or *BRCA2*, with estimated risks ranging from 36% to 46% for *BRCA1* mutation carriers and from 10% to 27% for *BRCA2* mutation carriers (1,2,5–7). Carriers of *BRCA1/2* mutations are counseled to help them interpret the implications of these elevated risks, choose strategies to reduce these risks, and maximize early detection of cancers. The risk of breast cancer can be reduced either with risk-reducing oophorectomy and/or mastectomy or nonsurgically (ie, with screening and prevention techniques). However, due to the lack of effective screening for ovarian cancer, risk-reducing salpingo-oophorectomy (RRSO) is usually strongly recommended to *BRCA1/2* mutation carriers once childbearing is complete.

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RRSO has also been demonstrated to decrease the risk of both breast and ovarian cancer in *BRCA1/2* mutation carriers (8–17). However, studies examining the extent of risk reduction have used different designs; some are retrospective case–control studies, whereas others used a prospective cohort design [reviewed by Kauff and Barakat (18)]. Even among prospective studies, the inclusion criteria and the definitions of follow-up time differ. In some studies, only unaffected mutation-positive women are included and followed up. In others, particularly when examining ovarian cancer risk, women with breast cancer are included. Such differences in study design can introduce biases (such as survival bias) and can have an impact on risk reduction estimates. For example, the reported efficacy of RRSO in reducing the risk of ovarian/fallopian tube cancers has varied from 71% to 96% (8,10,11,13,16,17). Although these estimates imply a substantial reduction in risk, this variability may affect the decisions of premenopausal women who are making a decision about whether to undergo a treatment that will cause abrupt and premature menopause. Patients and their physicians need as much information as possible regarding the efficacy of RRSO in reducing cancer risk to balance this benefit with the health risks caused by premature entry into menopause. Hence, we identified the published studies pertaining to the benefits of RRSO in terms of reducing cancer risk, assembled information on their design, and calculated summary risk reduction estimates associated with RRSO in *BRCA1/2* mutation carriers with the goal of aiding women and their clinicians in making cancer risk reduction decisions. Because randomized clinical trials of RRSO are likely not feasible and may not be ethically appropriate (19), we report the results of all observational case–control and cohort studies in the literature.

CONTEXT AND CAVEATS

Prior knowledge

Risk-reducing salpingo-oophorectomy (RRSO)—the removal of the fallopian tubes and ovaries to reduce the risks of breast and ovarian cancer—is a cancer prevention strategy used by many women who carry germline mutations in the *BRCA1* and/or *BRCA2* genes (*BRCA1/2*). However, the magnitude of the risk reductions in women with *BRCA1/2* mutations who have undergone RRSO compared with those who have not is unclear.

Study design

A fixed-effects meta-analysis of pooled results from 10 published reports of RRSO and the risks of breast and/or ovarian or fallopian tube cancer in *BRCA1/2* mutation carriers.

Contribution

RRSO was found to be strongly associated with substantial reductions in the risks of breast, ovarian, and fallopian tube cancers among women who carry mutations in *BRCA1* or *BRCA2*.

Implications

The summary risk reduction estimates should provide guidance to women in planning cancer risk reduction strategies.

Limitations

Data were not available to evaluate the effects of birth cohort, timing of surgery, or other factors that may influence the risk reduction estimates associated with RRSO. Women included in the studies were not representative of the general population.

From the Editors

Methods

Search Strategy

To identify all reports of RRSO in *BRCA1/2* mutation carriers, we searched the PubMed database using the search terms "oophorectomy" and "BRCA1" or "BRCA2." This search yielded 346 studies that were published between January 1999 and December 2007: 309 that included the term "BRCA1" in the title and 267 that included the term "BRCA2" were identified. We then evaluated the full text of these citations to identify articles presenting primary data that provided estimates of risk reduction due to RRSO. No publications were excluded based on quality, sample size, language of publication, or other objective criteria related to study design and analysis. However, some publications that reported RRSO in *BRCA1/2* mutation carriers were not included because they did not estimate risk reduction. These included case reports, psychosocial or behavioral studies, commentaries, and clinical recommendations. Because the number of *BRCA1/2* mutation carriers is relatively limited and most research groups studying these women are in routine communication and collaborate with one another, we also undertook personal communications with all of the researchers or consortia that have large series of *BRCA1/2* mutation carriers and were known to have data that could have been used to report data on this topic. This search did not reveal any additional unpublished studies.

Statistical Analysis

Data were obtained from published estimates as published in the original articles. We undertook a fixed-effects meta-analysis using the hazard ratios (HRs) and/or odds ratios (as published in the original reports) to estimate the pooled relative risks and 95% confidence intervals (CIs). When two or more studies had overlapping study samples, we included only one published report from each group. Of the studies identified here, sample overlaps were noted in the studies of Rebbeck et al. (8,9), Domchek et al. (13), and Kauff et al. (16) and in those of Kauff et al. (10,16). Therefore, only Kauff et al. (16), which had the largest sample size of these five studies, was chosen for inclusion in the meta-analysis. There were no apparent overlaps among the other datasets, although we cannot rule out the possibility that a few individuals had participated in more than one study.

We carried out separate meta-analyses in *BRCA1* mutation carriers, *BRCA2* mutation carriers, and among women who carried either *BRCA1* or *BRCA2* mutations (denoted *BRCA1/2*). A chi-square test of homogeneity among the individual risk ratio estimates of the identified studies was also performed. To evaluate potential for publication bias, we used the adjusted rank correlation test of Begg and Mazumdar (20). All analyses were conducted using STATA/SE v9.0 (StatCorp, College Station, TX).

Results

The studies that formed the basis of this meta-analysis included case–control studies as well as prospective and retrospective cohort studies (Table 1). As can be seen in this summary, limitations of the currently available data regarding RRSO in *BRCA1/2* mutation carriers include variable study designs, small sample sizes for individual studies, many of which are retrospective in

Table 1. Published studies of risk-reducing salpingo-oophorectomy and cancer risk in *BRCA1/2* mutation carriers*

Study, first author, and year (reference)	Study design†	Patient source	No. with/without RRSO			Reported follow-up	Mean age at breast cancer (y)	Mean age at ovarian cancer (y)	Mean age at RRSO (y)
			BRCA1	*BRCA2*	*BRCA1/2*				
Rebbeck et al., 1999 (9)	RC	NAMC	43/79	NA	43/79	5546 PY	B1: RRSO: 44.7 B1: No RRSO: 43.4 B1/2: RRSO: 54.5	NR B1/2: RRSO: 39.8	B1: 36.8
Kauff et al., 2002 (10)	PC	SIS	56/48	42/24	98/72	2.0 MYFU	B1/2: No RRSO: 48.3 B1/2: RRSO: 52.5	B1/2: No RRSO: 51.2 B1/2: RRSO: 54.9	B1/2: 48.1
Rebbeck et al., 2002 (8)	RC	IMC	219/240	42/52	261/292	8.5 MYFU	B1/2: No RRSO: 50.3	B1/2: No RRSO: 50.3	B1/2: 42.0
Rutter et al., 2003 (17)	CC	ISMC	5/168	0/56	5/223	NA	NR	NR	NR
Eisen et al., 2005 (15)	CC	IMC	129/2341	36/786	166/3139	NA	B1: 38.9 B2: 40.9	NR	NR
Kramer et al., 2005 (12)	PC	NAMC	33/65	NR	NR	16.5 MYFU, 11,105 PY	B1: RRSO: 47.4 B1: No RRSO: 46.5 B1/2, RRSO: 47.8	NR B1/2: RRSO: 44.0	NR
Domchek et al., 2006 (13)	PC	IMC	103/191	52/80	155/271	2.5 MYFU	B1/2: No RRSO: 41.7	B1/2: No RRSO: 48.3 B1/2: RRSO: 51.1	B1/2: 44.8
Finch et al., 2006 (11)	RC	IMC	834/546	207/233	1041/779	3.5 MYFU	NR	B1/2: No RRSO: 53.8	B1/2: 46.4
Chang-Claude et al., 2007 (14)	RC	EMC	NR	NR	55/1601	65,675 PY	B1/2: 50.1 B1: RRSO: 49.8 B1: No RRSO: 44.0 B2: RRSO: 52.5	NR B1: RRSO: 46.4 B1: No RRSO: 56.2 B2: RRSO: NA	NR B1: 46.2 B2: 48.8
Kauff et al., 2008 (16)	PC	IMC	325/173	184/110	509/283	3.2 MYFU	B2: No RRSO: 53.0	B2: No RRSO: 64.0	

* In all but one of the prospective cohort studies, women with a prior diagnosis of breast cancer were included for the ovarian endpoint. In Domchek et al. (13) all patients were unaffected with breast or ovarian cancer at the start of follow-up, as the study was designed to evaluate the impact of RRSO on cancer incidence as well as disease-specific and overall survival. B1 = *BRCA1* mutation carriers; B2 = *BRCA2* mutation carriers; B1/2 = combined *BRCA1* or *BRCA2* group; PC = prospective cohort; RC = retrospective cohort; CC = case–control; NAMC = North American Multicenter Cohort; SIS = single-institution study; IMC = International Multicenter Cohort; ISMC = Israeli Multicenter Cohort; EMC = European Multicenter Cohort; MYFU = mean years of follow-up; PY = person-years; NR = not reported; and NA = not applicable; RRSO = risk-reducing salpingo-oophorectomy.

† In the original publications, the prospective and retrospective cohorts were analyzed by survival/failure time analysis methods; the case–control studies were analyzed by logistic regression.

nature, and short post-RRSO follow-up times in prospective studies. Eight studies (8-10,12-16) estimated the risk of breast cancer in BRCA1/2 mutation carriers who were treated with RRSO relative to BRCA1/2 mutation carriers who did not receive this treatment (Table 2). As summarized in Table 3 and Figure 1, three nonoverlapping studies (14–16), which included 5703 participants, estimated the risk of breast cancer in *BRCA1/2* mutation carriers who received RRSO relative to *BRCA1/2* mutation carriers who did not receive the procedure, giving a summary HR estimate of 0.49 (95% CI = 0.37 to 0.65). Four nonoverlapping studies (12,14–16) estimated the risk reduction associated with RRSO for breast cancer in *BRCA1* mutation carriers, giving a summary HR estimate of 0.47 (95% CI = 0.35 to 0.64). Finally, three nonoverlapping studies (14–16) estimated the relative risk for breast cancer in *BRCA2* mutation carriers, giving a summary HR estimate of 0.47 (95% CI = 0.26 to 0.84) (Table 3, Figure 1).

Six studies (8,10,11,13,16,17) (Table 2) estimated the risk of gynecologic cancer in *BRCA1/2* mutation carriers treated with RRSO relative to *BRCA1/2* mutation carriers who did not receive this treatment. Based on data from the three nonoverlapping datasets (11,16,17), which included 2840 participants, the summary HR was 0.21 (95% CI = 0.12 to 0.39) (Table 3, Figure 1). Only one study (16) estimated the risk of gynecologic cancer in *BRCA1* mutation carriers treated with RRSO relative to untreated *BRCA1* carriers (HR = 0.15, 95% CI = 0.04 to 0.56) (Table 2). No study estimated the risk reduction associated with RRSO in *BRCA2* mutation carriers. Kauff et al. (16) did investigate risk reduction in 294 women with *BRCA2* mutations, but observed no post-RRSO gynecologic cancers in this sample.

We found no evidence of publication bias of any of our estimates based on the Begg and Majumder test statistics presented in Table 3. No evidence of study heterogeneity was found based on the χ^2 test (Table 3).

Discussion

The clinical management of cancer risk in *BRCA1* and *BRCA2* mutation carriers is complex and should consider patient preferences; these preferences can be informed by accurate knowledge of the risks and benefits of the interventions considered (Table 4). The results of our meta-analysis suggest an 80% reduction in ovarian/fallopian tube cancer risk and a 50% reduction in breast cancer risk associated with RRSO in women who carry mutations in *BRCA1* or *BRCA2*. The consistency of these findings across the included studies confirms the strong association of RRSO with reduced risks of breast and ovarian cancer in *BRCA1* or *BRCA2* mutation carriers. In addition, modeling studies have also demonstrated that salpingo-oophorectomy has a large effect on years of life added, particularly when adjusted for quality of life (31). Furthermore, in a prospective study with short-term follow-up, RRSO was associated with a 90% reduction in breast cancer–specific mortality, a 95% reduction in gynecologic cancer–specific mortality, and a 76% reduction in overall mortality (13). Therefore, all of the available data demonstrate the utility of salpingo-oophorectomy in this population of patients.

Despite the consistent evidence favoring RRSO in women with mutations in *BRCA1* or *BRCA2*, the existing data remain somewhat

Table 2. Published studies of risk-reducing salpingo-oophorectomy and cancer risk in *BRCA1/2* mutation carriers*

Study, first author, and year (reference)	Ovarian and/or fallopian tube cancer by mutation status			Breast cancer by mutation status		
	BRCA1/2	*BRCA1*	*BRCA2*	*BRCA1/2*	*BRCA1*	*BRCA2*
Rebbeck et al., 1999 (9)	NA	NA	NA	NA	HR = 0.53 (0.33 to 0.84), N = 122†	NA
Kauff et al., 2002 (10)	HR = 0.15 (0.02 to 1.31), N = 170†	NA	NA	HR = 0.32 (0.08 to 1.20), N = 131†	NA	NA
Rebbeck et al., 2002 (8)	HR = 0.04 (0.01 to 0.16), N = 551†	NA	NA	HR = 0.47 (0.29 to 0.77), N = 241†	NA	NA
Rutter et al., 2003 (17)	OR = 0.29 (0.12 to 0.73), N = 251	NA	NA	NA	NA	NA
Eisen et al., 2005 (15)	NA	NA	NA	OR = 0.46 (0.32 to 0.65), N = 3305	OR = 0.44 (0.29 to 0.66), N = 2432	OR = 0.57 (0.28 to 1.15), N = 873
Kramer et al., 2005 (12)	NA	NA	NA	NA	HR = 0.38 (0.15 to 0.97), N = 98	NA
Domchek et al., 2006 (13)	HR = 0.11 (0.03 to 0.47), N = 426†	NA	NA	HR = 0.36 (0.20 to 0.67), N = 426†	NA	NA
Finch et al., 2006 (11)	HR = 0.20 (0.07 to 0.58), N = 1828	NA	NA	NA	NA	NA
Chang-Claude et al., 2007 (14)	NA	NA	NA	HR = 0.56 (0.29 to 1.09), N = 1601	HR = 0.50 (0.24 to 1.04), N = 1187	HR = 0.40 (0.07 to 2.44), N = 414
Kauff et al., 2008 (16)	HR = 0.12 (0.03 to 0.41), N = 792	HR = 0.15 (0.04 to 0.56), N = 498	HR = 0.00,‡ N = 294	HR = 0.53 (0.29 to 0.96), N = 597	HR = 0.61 (0.30 to 1.22), N = 368	HR = 0.28 (0.08 to 0.92), N = 229

* Hazard ratios (HRs), odds ratios (ORs) (with 95% confidence intervals), and sample size (N) are presented. All *P* values are two-sided. NA = not applicable.

† Not included in summary HR estimate because the sample set overlaps with that of other reports. Studies included in the summary estimate were chosen to maximize the sample size (power) of the meta-analysis.

‡ No postsurgery events were observed; 95% CI could not be estimated.

limited in a number of ways. First, the influence of cohort effects on cancer risk over time remain unclear, despite evidence that differences in risk over time may reflect changing exposures, lifestyle, reproductive history, and use of screening or preventive surgeries (32). We lacked the data necessary to evaluate the effects of birth cohort, timing of surgery, or other factors that may influence the risk reduction estimates associated with RRSO. Therefore, at this time it is difficult to infer whether specific cohorts, exposure groups, or other strata may experience different risk reduction effects than others.

To limit the possibility that reporting bias influenced our findings, we included all published studies of RRSO in *BRCA1/2*

Table 3. Summary estimates for ovarian/fallopian tube cancer and breast cancer risk reduction associated with salpingo-oophorectomy in *BRCA1/2* mutation carriers*

Summary characteristic	Ovarian and/or fallopian tube cancer by mutation status			Breast cancer by mutation status		
	BRCA1/2	*BRCA1*	*BRCA2*	*BRCA1/2*	*BRCA1*	*BRCA2*
Studies included	(11,16,17)	NA	NA	(14–16)	(12,14–16)	(14–16)
HR (95% CI)	0.21 (0.12 to 0.39)	NA	NA	0.49 (0.37 to 0.65)	0.47 (0.35 to 0.64)	0.47 (0.26 to 0.84)
P value for heterogeneity among studies†	.999	NA	NA	.998	1.000	.604
P value for publication bias‡	.999	NA	NA	.602	.176	.602

* NA = not applicable; HR = hazard ratio; CI = confidence interval.

† Derived from χ^2 test.

‡ According to Begg and Mazumder (20).

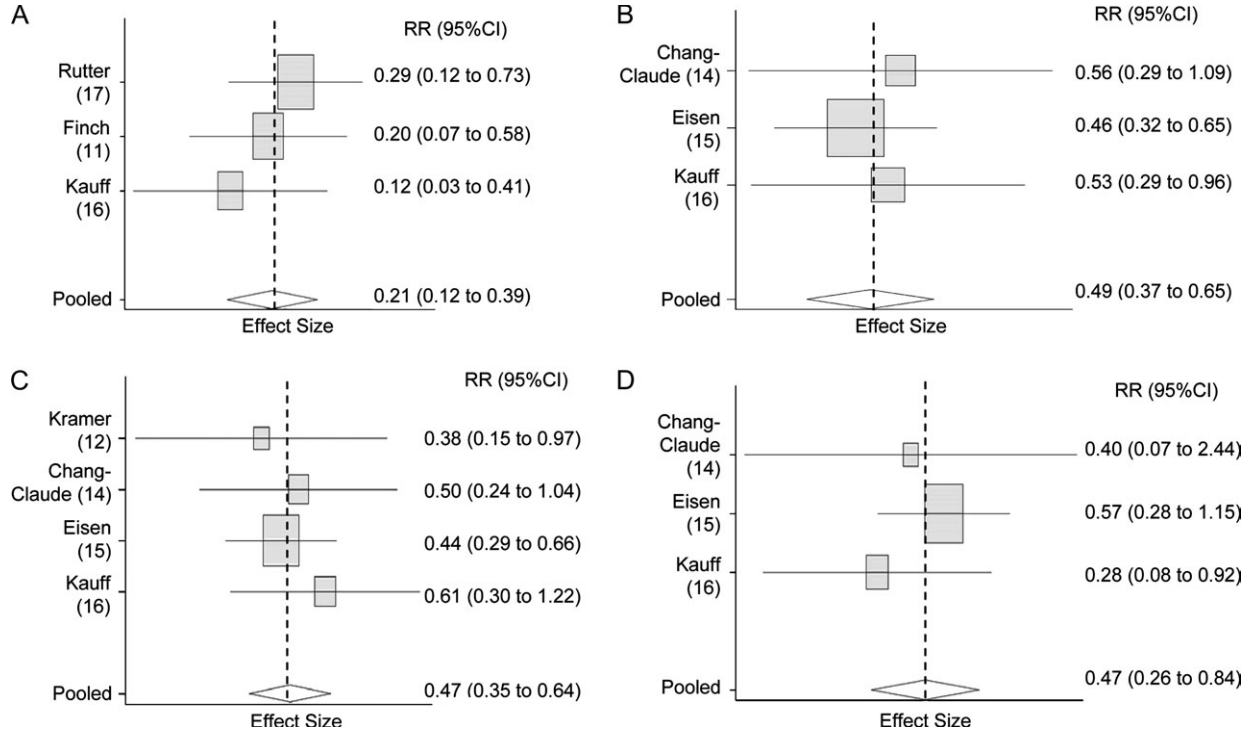

Figure 1. Forest plots of relative risk (RR) estimates for risk reduction associated with risk-reducing salpingo-oophorectomy (RRSO). **A**) Ovarian cancer risk reduction in *BRCA1/2* mutation carriers. **B**) Breast cancer risk reduction in *BRCA1/2* mutation carriers. **C**) Breast cancer risk reduction in *BRCA1* mutation carriers. **D**) Breast cancer risk reduction in *BRCA2* mutation carriers. The **box** sizes reflect the relative sample sizes of the individual studies; **horizontal lines** represent 95% confidence intervals (CIs). **Diamonds** represent the pooled point estimate and 95% confidence intervals. **Vertical dashed lines** represent the pooled relative risk estimate. Estimates less than a value of 1.0 suggest a favorable reduction in cancer risk associated with RRSO.

mutation carriers. However, we did not include any studies that reported the association of RRSO with cancer risk without providing estimates of risk reduction because these data would not contribute to pooled estimates of risk reduction. Because some studies included in the this analysis were limited in sample size and statistical power, their effect estimates for RRSO were large but not statistically significant, suggesting that a meta-analysis and presentation of summary statistics was appropriate. Two studies (15,17) were included in the summary estimates even though they used case–control designs, and therefore they yielded odds ratios

Table 4. Synopsis of management strategies available to *BRCA1* and *BRCA2* mutation carriers*

Management option	Strategy	Advantage	Limitation
Gynecologic cancer			
Chemoprevention	Oral contraceptive pills	Likely 30%–60% reduction in ovarian cancer risk (21,22)	Potential increase risk of breast cancer (23,24)
Screening	Transvaginal ultrasound, serum CA-125	Avoids RRSO	Unproven efficacy (25)
Risk-reducing surgery	Bilateral salpingo-oophorectomy	Substantial decrease in risks of ovarian and fallopian tube cancers (this study)	Premature menopause and iatrogenic infertility
Breast cancer			
Chemoprevention	Selective estrogen receptor modulators (tamoxifen, raloxifene)	May reduce risk of ER-positive breast cancer (26,27)	Very limited data in *BRCA1/2* mutation carriers
Screening	Yearly MRI Yearly mammogram		Issues of specificity (false positives)
	Self breast examination, clinical breast examination	≈80% sensitive for detection of malignancy (28,29)	Does not prevent cancer, goal is early detection
Risk-reducing surgery	Bilateral salpingo-oophorectomy	Substantial decrease in breast cancer risk (this study)	Premature menopause, iatrogenic infertility
	Mastectomy, with or without breast reconstruction	Highly effective (30)	Body image and quality-of-life issues

* RRSO = risk-reducing salpingo-oophorectomy; ER = estrogen receptor; MRI = magnetic resonance imaging.

rather than hazard ratios. Although odds ratios may slightly overestimate the risk reduction associated with RRSO, the annual incidence of ovarian and breast cancer in *BRCA1/2* mutation carriers is no more than 2%–4%, with the result that odds ratios are likely to be similar to hazard ratios in this setting.

Some of the variability in the individual study estimates reported may reflect study design differences, including the use of retrospective vs prospective samples and poorly characterized selection biases. Despite these differences, we noted no statistically significant heterogeneity in the estimates of risk reduction after RRSO. In addition, cohort studies estimated a greater reduction in cancer risk associated with RRSO (particularly ovarian/fallopian tube cancers) compared with the case–control studies (Table 1). As a result, there is some variability in the estimates obtained using case–control and cohort studies; nonetheless, the estimates all consistently reflect risk reduction associated with RRSO.

We have included all of the large collaborative group studies that addressed the question of reduced risk conferred by RRSO and whose study populations come from and are representative of mutation carriers in North America and Europe. No studies of RRSO in nonwhite populations have been reported, and additional data may be needed to understand the role of RRSO in these groups. Finally, the samples of women with *BRCA1/2* mutations reported here represent those who have generally been identified through high-risk clinics. Thus, these women may not be representative of the general population. However, they do represent the population of women who receive genetic testing and may be candidates for RRSO. Therefore, the populations summarized here represent the most relevant group in whom RRSO may be applied at this time.

Despite the strength and consistency of the data in the literature as reflected in our meta-analysis, a number of questions remain. There are only a few estimates of the association of RRSO with cancer risk in populations composed exclusively of *BRCA1* mutation carriers or *BRCA2* mutation carriers (12,14–16), and it is critical to understand how risk reduction may differ by gene. Using a prospective cohort approach and a large consortium dataset, we recently estimated gene-specific risks and found that hormonal modulation by RRSO may be associated with a greater reduction in breast cancer risk in *BRCA2* mutation carriers than in *BRCA1* mutation carriers (16). In contrast, the studies that used retrospective cohort (14) or case–control approaches (14,15) did not observe this difference, and therefore, there was no difference in the pooled estimates of breast cancer risk reduction reported in Table 1. Thus, differences in study design may influence the inferences we can make about the differences in risk reduction associated with RRSO in *BRCA1* vs *BRCA2* mutation carriers. The potentially larger risk reduction associated with RRSO in *BRCA2* vs *BRCA1* mutation carriers is of interest, given the high proportion of estrogen receptor (ER)–negative breast tumors in *BRCA1* mutation carriers compared with *BRCA2* mutation carriers (33). Our observation of a higher risk in *BRCA2* mutation carriers should be followed up in larger studies that specifically evaluate tumor markers. In addition, attention needs to be given to the time interval between RRSO and breast cancer diagnosis. For example, it is possible that there is greater breast cancer risk reduction in *BRCA2* mutation carriers, in whom the majority of tumors are ER positive, given that RRSO may treat some subclinical breast tumors. In contrast, in *BRCA1* mutation carriers, who have predominantly ER-negative breast cancer, it is unclear whether a "treatment effect" may exist, and any primary prevention effect may require more time to emerge.

Finally, the effect of age at RRSO on cancer risk reduction remains unresolved. Eisen et al. (15) reported that the breast cancer risk reduction with RRSO was greater in *BRCA1/2* mutation carriers who underwent surgery before age 50 than in women who underwent surgery after age 50. Among *BRCA1* mutation carriers older than age 50, no risk reduction was evident with RRSO. No statistically significant association of RRSO at any age with risk reduction was observed in *BRCA2* mutation carriers. Although these findings are consistent with effects of removal of hormone exposures in premenopausal women and not in postmenopausal women, the sample sizes in this analysis (15) were relatively small. Thus, additional studies are required to resolve the optimal age at surgery.

The importance of understanding the optimal age at which a woman should consider RRSO is underscored by a recent study (34) conducted in the general population that suggests that RRSO in women younger than age 45 is associated with an increased mortality, particularly if hormone replacement therapy (HRT) is not used. An initial report of HRT use after RRSO suggests that women can undergo RRSO and take HRT for a short time if needed after surgery because breast cancer risk is not substantially elevated in HRT users after RRSO (35). Although data on postmenopausal women do not demonstrate a cardiovascular benefit from HRT (36), an important limitation of this study (36) was the older age of the participants. More recent data have suggested that younger women going through natural menopause may indeed derive a cardiovascular benefit from HRT (36,37), and it is possible that *BRCA1/2* mutation carriers undergoing abrupt surgical menopause to reduce ovarian cancer risk who receive HRT may in fact derive important cardiovascular, bone health, and quality-of-life benefits. Although the risk–benefit ratio of RRSO is very different in *BRCA1/2* mutation carriers than in the general population, and RRSO in *BRCA1/2* mutation carriers has been associated with improved overall survival in the short term, these studies pointing to the potentially complex relationship of RRSO and HRT exposure raise important and difficult questions. For example, it is not yet clear whether the long-term effects of long-term HRT in unaffected mutation *BRCA1/2* carriers will ultimately be more beneficial in preventing noncancer mortality in these women or more harmful by increasing their risk of breast cancer (or potentially increasing cardiovascular events) compared with the general population. Given this possibility, studies that address the type, timing, and length of administration of HRT as well as its long-term effects on the association between RRSO and cancer risk and on other health factors in *BRCA1/2* mutation carriers are urgently needed. In the interim, we provide a summary of clinical recommendations related to the detection and prevention of cancer in *BRCA1/2* mutation carriers (Table 4).

Finally, although RRSO has become the standard of care for cancer risk reduction in women who have inherited *BRCA1/2* mutations, other options for risk reduction also exist. Women with

BRCA1/2 mutations who have been treated with risk-reducing mastectomy have a substantially reduced breast cancer risk (30). Furthermore, a study of breast cancer screening that added yearly magnetic resonance imaging to screening mammography suggested that combination of these modalities may also have benefit in the early detection of breast cancer in this group of women (28).

In conclusion, the summary risk reduction estimates presented here confirm that *BRCA1/2* mutation carriers who have been treated with RRSO have a substantially reduced risk of both breast and ovarian cancer. However, residual cancer risk remains after surgery. Therefore, additional cancer risk reduction and screening strategies are required to maximally reduce cancer incidence and mortality in this high-risk population.

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