clinical reviews

Risk-Reducing Bilateral Salpingo-Oophorectomy for Ovarian Cancer: A Review and Clinical Guide for Hereditary Predisposition Genes

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abstract

Pathogenic germline variants underlie up to 20% of ovarian cancer (OC) and are associated with varying degrees of risk for OC. For mutations in high-penetrance genes such as *BRCA1/2*, the role of risk-reducing bilateral salpingo-oophorectomy (RRSO) in cancer prevention is well-established and improves mortality. However, in moderate-penetrance genes where the degree of risk for OC is less precisely defined, the role of RRSO is more controversial. Although national guidelines have evolved to incorporate gene-specific recommendations, studies demonstrate significant variations in practice. Given this, our multidisciplinary group has reviewed the available literature on risk estimates for genes associated with OC, incorporated levels of evidence, and set thresholds for consideration of RRSO. We found that the benefit of RRSO is well-established for pathogenic variants in *BRCA1/2* as well as *BRIP1* and *RAD51C/D* where the risk of OC is elevated beyond our threshold for RRSO. In *PALB2*, RRSO is particularly controversial as newer studies consistently demonstrate an increased risk of OC that is dependent on family history, making uniform recommendations challenging. Additionally, new guidelines for Lynch syndrome provide gene-specific risks, questioning the role of RRSO, and even hysterectomy, for *MSH6* and *PMS2* mutation carriers. Given these uncertainties, shared decision making should be used around RRSO with discussion of individual risk factors, family history, and adverse effects of surgery and premature menopause. Herein, we provide a clinical guide and counseling points.

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INTRODUCTION

Ovarian cancer (OC) is the fifth leading cause of cancer-related deaths in the United States, with a 5-year mortality of 48.6%.[1] Screening is not effective for OC,[2] and most women are diagnosed with advanced disease.[3] OC is a heterogenous disease, reflecting malignancies of various epithelial pathologies and origins including fallopian tube and primary peritoneal cancers.[4] An underlying inherited cancer syndrome may be present in up to 20% of patients with OC.[5] Mutations in genes encoding proteins critical for homologous recombination, including *BRCA1/2*,[6] confer increased risk of high-grade serous OC (HGSC),[7-9] whereas mutations in mismatch repair genes confer increased risk of OC histologic types associated with endometriosis (eg, endometrioid and clear cell histology).[10-13] In addition, these genes are individually categorized as high penetrance, conferring a high lifetime risk for OC that is well-established in the literature, or moderate penetrance, associated with varying degrees of risk that are not uniformly agreed upon.[9] In the high-penetrance *BRCA1/2* genes, risk-reducing bilateral salpingo-oophorectomy (RRSO) decreases the incidence of OC and improves mortality.[14-16]

More recent studies have improved our understanding of inherited OC risk beyond *BRCA*-related Hereditary Breast and Ovarian Cancer and have provided more refined estimates of OC risk for many moderate-penetrance genes including *BRIP1*, *RAD51C/D*, *PALB2*, and *ATM*.[17,18] In contrast to *BRCA1/2*, there is still much controversy regarding the degree of conferred risk for OC and whether that risk is sufficiently elevated above the general population to warrant consideration of RRSO.[19] However, a recent analysis of the Prospective Registry Of Multiplex Testing (PROMPT), a national online registry for individuals with germline variants detected via multigene panel testing, found that 10%-15% of women with germline variants in moderate-penetrance genes (*ATM*, *PALB2*, and *CHEK2*) were undergoing RRSO, despite a paucity of data on benefits of RRSO in this setting,[20] which is particularly concerning for individuals with variants in *CHEK2*, for which there is no established OC risk.[9] Many of these women were premenopausal (66.7% for *ATM*, 35.3% for *PALB2*, and 59% for *CHEK2*) and had no family history of OC,[20] highlighting the need for clinical guides in an area of uncertainty.

However, the risk for OC associated with mutations in moderate-risk genes is variable and often depends on

ASSOCIATED CONTENT

Appendix

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family history; therefore, the role of risk-reducing surgery in individuals with mutations in moderate-penetrance genes is less clear. Furthermore, genes that were initially classified as moderate to high risk for OC are now being recategorized into lower risk categories. Specifically, recent National Comprehensive Cancer Network (NCCN) guidelines for Lynch Syndrome[21] now provide gene-specific guidelines for RRSO and hysterectomy (HYS), citing insufficient evidence to recommend RRSO for *MSH6* and insufficient evidence with potentially no elevated risk of OC for *PMS2*.

A recent survey of members of the Society of Gynecologic Oncology found that although recommendations and practices regarding RRSO for high-penetrance genes were consistent, there was significant variation in rates of RRSO with respect to moderate- and low-penetrance genes. The group highlighted a need for better data and guidelines to inform clinical practice.[22] Herein, we review the data estimating the risk of OC associated with high- and moderate-penetrance genes and recommendations regarding RRSO, while providing a clinical guide for physicians to comprehensively evaluate the risks and benefits of RRSO and engage in shared decision making with patients.

DEVELOPMENT OF A CLINICAL GUIDE FOR RRSO IN OC

To help clinicians understand the different levels of OC risk conferred by various genes and discuss RRSO in the context of this uncertainty, our multidisciplinary team created a clinical guide from available evidence to facilitate discussion of RRSO, Figure 1. The *y*-axis represents estimated cumulative lifetime risk of OC. The *x*-axis represents increasing level of evidence for OC risk and benefit from RRSO with implicated genes plotted accordingly. The population-level lifetime absolute risk of OC is estimated to be 1%-2%[23] and is depicted to provide a baseline level of risk. Previous studies have suggested an RRSO threshold of double the population risk or 2.64%.[19] This is less than the risk of OC conferred by having a first-degree relative with OC, plotted on the far left, which is estimated at a cumulative lifetime risk of 3%-4%.[24] However, these individuals are not routinely recommended RRSO currently[24] and new data in the area of multigene panels are needed to better define this risk. Additionally, RRSO has been shown to be cost-effective at a lifetime cumulative risk for OC of 4% or more.[25] Taking all these considerations into account, our group has recommended an RRSO threshold range of 3%-4% and we posit that in genes conferring a cumulative lifetime risk of OC above this threshold, the benefits of RRSO would outweigh the risks. This threshold is based on currently available evidence and may change over time and/or require adjustment in certain situations. We provide a range with errors to depict risks associated with each gene to reflect the uncertainty around these risk estimates and potential changes over time as more data accumulate. Color-coded arrows depict recommended age of RRSO on the basis of NCCN recommendations, highlighting areas of controversy and insufficient data.[19] Studies have shown that positive family history can influence the magnitude of this risk, and therefore, the age at which to consider RRSO should be adjusted on the basis of family history.[24] Finally, this clinical guide is limited by the data used to derive it, which are subject to biases inherent to case-control and even prospective or family studies and should be interpreted cautiously.

RECOMMENDATIONS FOR *BRCA1/2*

Germline mutations in *BRCA1/2* are present in 10%-15% of women with OC[26] and are associated with increased risk of HGSC.[8] The cumulative lifetime risk of HGSC (age 70-80 years) approaches 40% in *BRCA1* and 20% in *BRCA2* mutation carriers.[7,8] RRSO decreases the incidence of HGSC and improves mortality,[14-16] with Cochrane reviews finding a 68% reduction in overall mortality and 94% reduction in OC-associated mortality.[14] A small residual risk of primary peritoneal cancer after RRSO remains (3%-4%), especially in *BRCA1* mutation carriers.[14,27-30] Importantly, the cancer-reducing benefits of RRSO must be balanced with increased morbidity from premature menopause.[31,32] The increased risk of OC manifests at a later age in *BRCA2* compared with *BRCA1* mutation carriers.[8] Accordingly, the NCCN recommends RRSO between age 35 and 40 years for *BRCA1* mutation carriers, whereas for *BRCA2* carriers, delaying until age 40-45 years is reasonable,[33] Table 1.

RECOMMENDATIONS FOR *BRIP1/RAD51C/RAD51D*

BRIP1 encodes a protein integral to repair of double-stranded DNA breaks,[6] and pathogenic germline variants are present in 1% of all patients with OC.[5] Multiple studies have demonstrated that pathogenic variants in *BRIP1* confer an increased risk of OC, with estimated relative risks ranging from 2.62 to 11.2.[34-39] A study specifically examining loss-of-function *BRIP1* variants (mostly truncating) found an even higher estimate of OC risk, OR 19.17 (95% CI, 11.13 to 33).[40] The cumulative lifetime risk up to age 80 years of OC ranges from 4% to 13%.[34-38] OC risk started to diverge from population level at around age 50 years.[38]

RAD51C/RAD51D encodes proteins essential for homologous recombination,[6] and pathogenic germline variants are present in 0.5%-0.8% of all patients with OC.[5] Studies have clearly demonstrated an increased risk of OC, with relative risk estimates ranging from 3.4 to 14.6 for *RAD51C*[34,36,37,39,41-43] and 4.78 to 12.0 for *RAD51D*.[34,36,37,39,41-43] Lifetime cumulative risks of OC are estimated to range from 4% to 18% for both genes, with a recent segregation analysis in families with *RAD51C/D* mutations estimating the cumulative risk of OC up to age 80 years to be 11% for *RAD51C* and 13% for *RAD51D*.[43] This risk appears to diverge from population-level risk at around age 50 years.[43] The lifetime risk of OC may also be higher

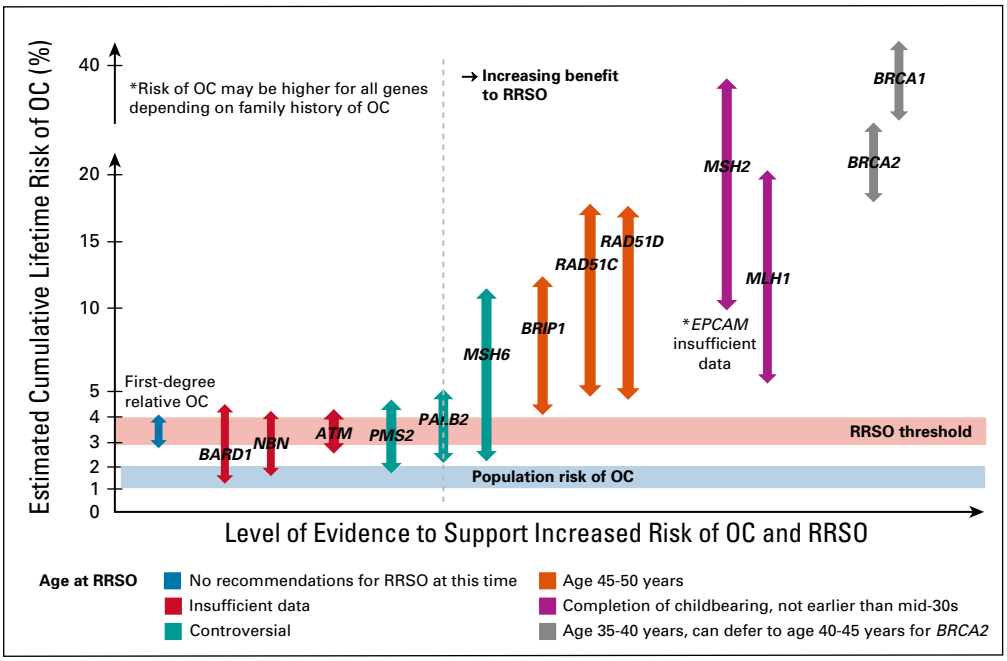

FIG 1. Clinical guide for RRSO for OC by cancer susceptibility gene (decision aid for RRSO for OC in moderate-penetrance genes). This figure provides a clinical guide to assess benefit of RRSO for OC on the basis of the cancer susceptibility gene implicated. The *y*-axis represents estimated cumulative lifetime risk of OC, and the *x*-axis represents increasing risk for OC and evidence to support RRSO. Population risk for OC (1%-2%) and RRSO threshold (3%-4%) are plotted. Mutations in genes to the right of the dotted line represent clinical situations where there is likely benefit to RRSO for mutation status alone. Genes that overlap the RRSO threshold require careful consideration of risks and benefits of RRSO, considering family history, individual risk factors, risks of RRSO and premature menopause, and patient preference. Color coding indicates the age to consider RRSO on the basis of age at which increased risk starts to exceed population-level risk and areas of controversy and insufficient data. NOTE. It is reasonable to consider RRSO earlier than the recommended age in those with a significant family history of OC, typically 5-10 years before the earliest diagnosed OC. OC, ovarian cancer; RRSO, risk-reducing bilateral salpingo-oophorectomy.

(approximately 30%) in those mutation carriers with a family history of OC, which exceeds the risk of *BRCA2* mutation carriers and approaches that of *BRCA1* mutation carriers.[43]

Accordingly, the NCCN recommends consideration of RRSO for all *BRIP1* and *RAD51C/D* mutation carriers at age 45-50 years, Table 1.[33] As OC risk increases in those with a significant family history, it may be reasonable to consider RRSO at an earlier age in those with a significant family history of OC, typically 5-10 years before the earliest OC in the family.

RECOMMENDATIONS FOR *PALB2*

For other moderate-penetrance genes, reported risks of OC are more modest and the role and timing of RRSO are controversial. *PALB2* encodes a protein that binds *BRCA1/2* at sites of DNA damage,[6] and pathogenic germline variants in *PALB2* are found in 0.5% of all patients with OC.[5] Multiple studies consistently demonstrated an increased risk of OC,[9] with estimates of relative risk ranging from 1.22 to 4.4[34,36-39,44,45]; however, these initial studies had many limitations including insensitive sequencing methods, limited clinical data, and narrow populations, Appendix Table A1 (online only). A more recent segregation study in 524 families with pathogenic germline *PALB2* variants found that the OC relative risk ratio was 2.91. The lifetime cumulative risk of OC to age 80 years was 4.8% and was estimated to be higher (up to 10%) in those with a significant family history of OC.[46] This increased risk starts to diverge from population-level risk at age 50 years and exceeds twice the population-level risk between age 60 and 70 years. Another recent study of 5,914 OC cases and 5,479 controls of European ancestry found a 3-fold increase in risk for *PALB2* mutation carriers compared with controls.[47] Although the NCCN currently cites insufficient evidence to recommend routine RRSO on the basis of a *PALB2* mutation alone,[33] this is controversial as recent studies show a consistently elevated risk of OC, which crosses the risk threshold for consideration of RRSO after age 60 years.[46] Therefore, clinicians should facilitate an individualized discussion of the option of RRSO in *PALB2* mutation carriers with incorporation of family history and a personalized review of individual risks and benefits. If

TABLE 1. Summary of OC Risk and NCCN Guidelines for RRSO by Gene

Gene	Association With OC	Degree of OC Risk (%)[a]	Quality of Evidence[b]	NCCN Recommendation (V 1.2020, July 21, 2020)	Age at RRSO (years)
BRCA1	Yes	> 20	1	RRSO	35-40
BRCA2	Yes	> 10	1	RRSO	40-45
MLH1	Yes	> 10	2	Consider HYS/RRSO	After childbearing, not earlier than 35-40
MSH2	Yes	> 10	2	Consider HYS/RRSO	After childbearing, not earlier than 35-40
MSH6	Yes	3-10	2	Consider HYS, controversial for RRSO but potentially beneficial	
PMS2	Uncertain	3	2	Consider HYS, insufficient evidence for RRSO, potentially not beneficial	
EPCAM	Uncertain	Unknown	2, 3	Consider HYS/RRSO (insufficient evidence)	
BRIP1	Yes	> 10	2, 3	Consider RRSO	45-50
RAD51C	Yes	> 10	2, 3	Consider RRSO	45-50
RAD51D	Yes	> 10	2, 3	Consider RRSO	45-50
PALB2	Yes	3-5	2, 3	Controversial for RRSO	
ATM	Yes	3-4	3	Insufficient evidence for benefit of RRSO or controversial depending on family history	
NBN	Uncertain or mixed	NA	3	Insufficient evidence for benefit of RRSO	
BARD1	Uncertain	NA	3	Insufficient evidence for benefit of RRSO	
CHEK2	No	NA	2, 3	No RRSO indicated	

NOTE. It is reasonable to consider RRSO earlier than the recommended age in those with a significant family history of OC, typically 5-10 years before the earliest diagnosed OC. The table depicts various genes and association with OC, estimated levels of risk, strength of evidence, and current NCCN recommendations for RRSO with assessment of strength of evidence.

Abbreviations: HYS, hysterectomy; NCCN, National Comprehensive Cancer Network; OC, ovarian cancer; RRSO, risk-reducing bilateral salpingo-oophorectomy.

[a]Estimates of lifetime cumulative risk of OC may vary depending on family history.

[b]Oxford Centre for Evidence-Based Medicine Quality Rating.

RRSO is considered, it can be deferred until the age of natural menopause, which is an important discussion point when counseling these patients.[48]

RECOMMENDATIONS FOR *ATM*

ATM encodes for a protein involved in repair of double-stranded DNA breaks,[49] and multiple studies have shown a mild but consistently increased risk of OC in individuals with pathogenic germline variants. Estimates of relative risk range from 1.69 to 2.85[34,36,37,39,50,51] with a cumulative lifetime risk of 3%-4% (by age 70 years), although risk may be higher in those with a significant family history of OC.[34-37] Given this modest increased risk, which is comparable with the risk associated with having a first-degree relative with OC,[24] the NCCN cites insufficient evidence to recommend RRSO on the basis of a pathogenic germline *ATM* variant alone,[33] Table 1. However, discussion of risks and benefits on the basis of family history and individual risk factors is encouraged. If RRSO is pursued, it is reasonable to defer until around the time of natural menopause.

GENES WITH INSUFFICIENT EVIDENCE FOR ASSOCIATION WITH OC

Two additional genes involved in homologous repair, *BARD1* and *NBN*,[6] may have an association with OC; however, data are mixed and currently insufficient to form recommendations for RRSO.[9] Most estimates of risk are small, ranging from 1.72 to 2.3[34-39] for *NBN* and 0.59 to 4.2[34-39] for *BARD1*, although the higher risk might be confounded by individuals who carry both *BARD1* and *BRCA1* pathogenic germline variants.[9,34-37] *MRE11A* and *RAD50* also encode proteins integral to DNA repair,[6] and although included in some multigene panels, there is insufficient evidence to suggest an association with OC or any other cancers.[35-37] By contrast, *CHEK2* is a gene associated with increased breast cancer (BC) susceptibility but has not been shown to be associated with OC.[34-37] Therefore, RRSO for *CHEK2* mutation carriers is not recommended, Table 1.

RECOMMENDATIONS FOR MISMATCH REPAIR GENES

Lynch syndrome is caused by pathogenic germline variants in the DNA mismatch repair genes (*MLH1*, *MSH2*, *MSH6*,

PMS2, and *EPCAM*) and is associated with endometrial cancer (EC) and endometriosis-associated OC, Table 2.[10-13] Using large, prospective cohort studies, estimates of the cumulative lifetime risk of EC (age 70-80 years) range from 34% to 54% for *MLH1*,[11,12,52] 21% to 57% for *MSH2*,[11,12,52] and 16% to 49% for *MSH6* mutations,[11,12,52] although some studies state that the risk could be higher for *MSH6*.[53] Estimates of the cumulative lifetime risk (age 70-80 years) of OC range from 4% to 20% for *MLH1*[11,12,52] and 8% to 38% *for MSH2*[11,12,52] mutations. The risk is potentially lower (1%-13%) for *MSH6* mutations,[11,12,52] although other studies found similar rates of OC as *MSH2*.[54] Data are less robust for *PMS2* but support a lower associated risk of EC (cumulative lifetime risk of 13%-26%) compared with other DNA mismatch repair genes and an association with OC; however, these data are insufficient to precisely quantify that risk.[12,55-57] A limitation to these data is the heterogeneity and range of risk estimates. Additionally, many studies draw from the same, mostly European population, which may limit generalizability to all populations. Finally, as the rarely observed deletions of *EPCAM* result in *MSH2* promoter methylation and silencing,[58] risks of EC and OC are hypothesized to be similar to *MSH2* carriers,[59] although some studies suggest that EC risk may be lower (approximately 10%-15% cumulative lifetime risk) and dependent on the type of *EPCAM* deletion.[59,60] The risk of OC associated with *EPCAM* deletions is currently unknown.[61]

Previous NCCN guidelines recommended HYS and consideration of RRSO after completion of childbearing for all women with Lynch syndrome. Given the potentially lower risk of OC in *MSH6*,[11,52,62,63] the lower risk and older age of onset for EC in *PMS2*, and the uncertainty about OC risk in *PMS2*,[62,63] some groups have put forth gene-specific recommendations.[52,57] Accordingly, the current NCCN guidelines include gene-specific recommendations.[21] They cite insufficient evidence and need for individualized decision making for RRSO in *MSH6* and potentially no increased risk of OC for *PMS2* carriers.[21] However, international guidelines[64] and clinical practices vary. An international survey regarding risk-reducing practices in Lynch syndrome found global agreement (approximately 90%) in performing HYS/RRSO for *MLH1*, *MSH2*, and *MSH6* mutation carriers with less practitioners performing HYS/RRSO for *PMS2* (67%).[65] The uncertainty in the data and ambiguity inherent in these recommendations present a clinical challenge, and guidance is needed.

CLINICAL GUIDE COUNSELING POINTS

These studies demonstrate that as estimates of increased risk, albeit modest, are becoming more precise for these moderate-penetrance genes, guidance on how to discuss and appropriately select patients for RRSO is critical to avoid unnecessary procedures and associated morbidity, particularly in premenopausal women. Using our clinical guide, individuals with pathogenic variants in genes to the right of the dotted line are thought to benefit from RRSO. Those genes that overlap the RRSO threshold or have insufficient evidence (*PALB2*, *MSH6*, and *PMS2*) require careful discussion of risks and benefits, integrating family history and other clinical variables (eg, age of menarche, parity, hormonal therapies, history of endometriosis or polycystic ovarian syndrome etc)[66] that may affect an individual's risk for OC as well as patient preferences and levels of risk tolerance. In the future, polygenic risk scores may help to individualize cancer risks and aid in counseling.[67,68]

Other factors to consider include adverse effects of premature surgical menopause and the role of hormone replacement therapy (HRT). Premature menopause has been associated with detrimental effects on mood, sexual health, cognition and bone and cardiovascular health, and increased risk of other cancers.[31,32] In addition, the prospective nurse's health study found that oophorectomy before age 50 years was associated with increased mortality in those who did not use estrogen replacement.[69] HRT may be initiated in select patients after discussion of the risks and benefits, and for those with prior HYS, estrogen alone (*v* estrogen and progesterone) can be used, which might have a decreased risk of BC.[70-72] Given the associated risk of BC in many of these genes, HRT should be avoided in those with a history of BC, particularly hormone receptor–positive BC.[70,72]

Although data are currently insufficient to support salpingectomy alone for risk reduction, there are ongoing clinical trials (NCT02760849, NCT02321228, NCT04294927, NCT04251052, NCT01907789, and NCT01907789).[73,74] Beyond Lynch syndrome, careful discussion of the role of concurrent HYS with RRSO may also be necessary, both to prevent the slightly increased risk of serous type endometrial cancer in *BRCA* mutation carriers[75,76] and to facilitate usage of estrogen monotherapy as HRT.[72] Currently, there are insufficient data to recommend HYS on the basis of *BRCA* mutation status alone.[77] As many of these genes are also associated with increased risk of BC, it is reasonable to consider the effect of RRSO on BC risk in addition to OC risk. However, data to support this are currently limited to *BRCA1/2* carriers.[78,79] Finally, one must also address and balance psychosocial factors including family planning, perceived cancer risk, levels of distress or worry, and support and coping mechanisms in the context of decisions regarding RRSO and timing.[80,81]

In conclusion, although well-established in *BRCA1/2* and other high-penetrance genes, there is ongoing controversy over the role of RRSO in moderate-penetrance genes where lifetime risk of OC is modestly increased above the general population. We have reviewed and interpreted the available data examining associations of pathogenic variants in various genes with OC risk. To facilitate shared decision making, we have summarized national guidelines regarding RRSO and highlighted areas of controversy and limitations to the data. Our clinical

TABLE 2. Studies Reporting Risks of Endometrial Cancer and OC in Lynch Syndrome

Study	No.	Lifetime Age, Years	Lifetime Cumulative Incidence of EC, % (95% CI)				Lifetime Cumulative Incidence of OC, % (95% CI)				Cohort
			MLH1	*MSH2*	*MSH6*	*PMS2*	*MLH1*	*MSH2*	*MSH6*	*PMS2*	
Bonadona et al[11]	537 families	80	57 (22 to 82)	21 (9 to 82)	17 (8 to 47)	—	20 (1 to 66)	38 (3 to 81)	1 (0 to 3)	—	French Study of LS families
Baglietto et al[53]	113 families	80	—	—	44 (30 to 58)	—	—	—	—	—	International cohort from various registries and medical centers
Senter et al[56]	99	70	—	—	—	15 (6 to 35)	—	—	—	—	In-depth sequencing of *PMS2* in Lynch probands
Engel et al[54]	2,118	70	—	—	—	—	5	10	10	—	Pooled German and Dutch national Lynch Registries
Ten Broeke et al[57]	98 families	70	—	—	—	11.78 (2.6 to 20)	—	—	—	—	*PMS2*-specific families referred to Genetics center in Northern Europe
Møller et al[62]	1,942	70	34 (24 to 44)	51 (33 to 69)	49 (25 to 74)	24 (0 to 52.8)	11 (3.2 to 20)	15 (5.5 to 25)	0	0	Mallorca Group Prospective Lynch Cohort, international
Møller et al[12]	3,119	75	42.7 (33 to 52)	56.7 (42 to 72)	46.2 (27 to 65)	26.4 (0.8 to 52)	10.1 (4.8 to 15)	16.9 (5.7 to 28)	13.1 (0 to 31.2)	0	Mallorca Group Prospective Lynch Cohort, international
Dominguez-Valentin et al[63]	6,350	75	37 (30 to 47)	48.9 (40 to 61)	41.1 (29 to 62)	12.8 (5.2 to 50)	11 (7.4 to 20)	17.4 (12 to 32)	10.8 (3.7 to 39)	3 (0.5 to 44)	Mallorca Group Prospective Lynch Cohort, international

NOTE. Large cohort and case-control studies evaluating the risk of EC and OC associated with Lynch Syndrome genes were derived from PubMed searches using MESH terms Lynch syndrome, *MLH1*, *MSH2*, *MSH6*, *PMS2*, endometrial cancer, and ovarian cancer as well as expert opinion within our multidisciplinary group. This table depicts study characteristics and estimates of relative risk of EC and OC associated with each Lynch syndrome gene. Of note, many of these publications draw from the same population with varying cohort sizes and follow-up times, which may bias results and limit generalizability.

Abbreviations: EC, endometrial cancer; NA, not available; OC, ovarian cancer; LS, Lynch syndrome.

guide serves as a framework to assist clinicians in integrating the data, assessing degree of benefit, and facilitating individualized decision making around RRSO. As more data emerge for specific genes and risk estimates become more precise, this framework can be adjusted to reflect the changing clinical landscape.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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APPENDIX

TABLE A1. Summary of Studies Examining Risk of OC in *PALB2* Mutation Carriers

Study	No.	Type of Study (control population)	Relative Risk of OC (95% CI)	Cumulative Lifetime Risk	Study Characteristics and Limitations
Antoniou et al[44]	154 families	Family or segregation analysis	2.31 (0.77 to 6.97)	NA	Primarily looked at BC risk and limited number of OC cases
Ramus et al[38]	3,236 OC cases	Case-control (OC screening population)	$P = .08$ ($P = .045$ using UK Familial Cancer Screening Study Cases)	NA	Insensitive sequencing methods with low coverage and controls derived from high-risk screening group and potential to underestimate mutation frequencies
Kurian et al[34] (Myriad)	95,561 participants	Modeling and case-control (matched controls without cancer who underwent testing)	1.60 (0.98 to 2.60) Logistic Regression 3.00 (0.75 to 17.2) Case-Control	NA	Used matched controls from test participants referred for genetic testing who were unaffected at time of testing and biased controls
Norquist et al[37]	1,915 OC cases	Case-control (ESP/ExAC)	4.4 (2.1 to 9.1)	NA	Clinical trial population (GOG 218 and 262)
Lilyquist et al[36] (Ambry)	7,768 OC cases	Case-control (ExAc)	3.08 (1.93 to 4.67)	NA	Limited to European ancestry; authors performed sensitivity analysis with all ethnicities and pathogenic variants only with similar results
Suszynska et al[39]	120,000 OC and BC cases	Meta-analysis (gnomAD)	2.13 (1.4 to 3.2)	NA	Meta-analysis of multigene panel studies examining OC and BC risk
LaDuca et al[35] (Ambry)	12,602 OC cases	Case-control (gnomAD)	1.22 (0.66 to 2.21)	NA	Limited clinical data and pan-cancer analysis
Yang et al[46]	524 families	Family or segregation analysis	2.91 (1.4 to 6.04)	5% (up to age 80 years)	High-quality segregation analysis that calculated cumulative risk by decade of life. OC risk significantly increases at age 60 years and may be higher in those with a significant family history of OC
Song et al[47]	20,520 OC cases	Case-control	3.01 (1.59 to 5.68)	3.2% (1.8%-5.7%) up to age 80 years	European ancestry, test and validation cohorts, and targeted and whole-exome sequencing in some cases

Abbreviations: BC, breast cancer; ESP, Exome Sequencing Project; ExAC, Exome Aggregation Consortium; gnomAD, Genome Aggregation Database; NA, not available; OC, ovarian cancer.