A Systematic Review on Cost-effectiveness Studies Evaluating Ovarian Cancer Early Detection and Prevention Strategies

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ABSTRACT

Ovarian cancer imposes a substantial health and economic burden. We systematically reviewed current health-economic evidence for ovarian cancer early detection or prevention strategies. Accordingly, we searched relevant databases for cost-effectiveness studies evaluating ovarian cancer early detection or prevention strategies. Study characteristics and results including quality-adjusted life years (QALY), and incremental cost-effectiveness ratios (ICER) were summarized in standardized evidence tables. Economic results were transformed into 2017 Euros. The included studies ($N = 33$) evaluated ovarian cancer screening, risk-reducing interventions in women with heterogeneous cancer risks and genetic testing followed by risk-reducing interventions for mutation carriers. Multimodal screening with a risk-adjusted algorithm in postmenopausal women achieved ICERs of 9,800–81,400 Euros/QALY, depending on assumptions on mortality data extrapolation, costs, test performance, and screening frequency. Cost-effectiveness of risk-reducing surgery in mutation carriers ranged from cost-saving to 59,000 Euros/QALY. Genetic testing plus risk-reducing interventions for mutation carriers ranged from cost-saving to 54,000 Euros/QALY in women at increased mutation risk. Our findings suggest that preventive surgery and genetic testing plus preventive surgery in women at high risk for ovarian cancer can be considered effective and cost-effective. In postmenopausal women from the general population, multimodal screening using a risk-adjusted algorithm may be cost-effective.

Introduction

Ovarian cancer is a leading cause of gynecologic cancer–related death and the seventh most common cancer in women in developed countries (1, 2). North America and Western Europe are the countries with the highest incidences for ovarian cancer with age-standardized annual incidence rates of 8.1 (United States) and 7.5 (Europe) per 100,000 women reported for the year 2012, respectively (1).

Because early symptoms are rare, the majority of ovarian cancer cases are diagnosed at an advanced stage (3) associated with poor prognosis. The disease is therefore called a "silent killer" leading to substantial medical and financial burden for both the patient herself and the healthcare system as a whole (4). In the last decade, there has been some progress in ovarian cancer early detection and prevention. For women diagnosed with germline mutations, specific surveillance programs and risk-reducing prophylactic surgeries that may reduce cancer-associated mortality by up to 85% are currently recommended in most countries (5–8).

To date, there is no globally accepted ovarian cancer early detection program for women from the general population at average risk for ovarian cancer. However, recent results from the United Kingdom Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) reported a significant stage shift with annual multimodal screening using longitudinal cancer antigen biomarker CA-125 plus transvaginal ultrasound based on the Risk of Ovarian Cancer Algorithm (ROCA), which accounts for a rise in CA-125 relative to baseline (9). A trend for mortality reduction was reported, but results were not statistically significant at a median follow-up of 11.1 years. Of note, further *post hoc* analyses excluding prevalent cases at baseline resulted in statistically significant mortality reductions. Further results from the extended follow-up are awaited for by the end of 2019.

The increasing evidence on tubal origins of some ovarian cancers more and more leads to opportunistic bilateral

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salpingectomy at tubal ligation and hysterectomy in women from the general population (10, 11). More recent research is focusing on biomarkers predicting an individual's ovarian cancer risk using genetic and epidemiologic information that can be used for tailored prevention and individualized screening approaches (12).

Health care resources are becoming increasingly scarce, and consequently, decision makers have to make more and more difficult decisions regarding the allocation of these resources. Therefore, it is critical that both the effectiveness regarding patient-relevant outcomes and cost-effectiveness of new prevention or screening strategies are evaluated in the context of a specific health care system.

The purpose of this study was to systematically review the current evidence on long-term health-economic consequences of different early detection and prevention strategies for ovarian cancer in populations with heterogeneous risk profiles.

This review may aid health policymakers to make informed decisions regarding resource allocations and may serve as guidance toward an optimized and uniform ovarian cancer early detection and prevention concept in developed countries.

Methods

We systematically searched for full health-economic evaluation studies assessing both the clinical long-term effectiveness and cost-effectiveness of early detection and prevention strategies for ovarian cancer. We primarily focused on decision-analytic modeling studies that provide a quantitative approach to synthesize different clinical and economic short-term data (e.g., test performance, prognosis, quality-of life, economic data) and that can be used to evaluate the trade-off between benefits, harms, and costs of different alternative interventional strategies (13).

The search was performed in the electronic databases Medline (Ovid and PubMed), Embase (Ovid), the Cochrane Library, CRD databases [NHS EED (Economic Evaluation Database), DARE, HTA Database] and EconLit (last up-date: December 2019). The search codes were developed separately for each database using Mesh and search term combinations for ovarian cancer, detection or prevention, effectiveness, costs, and modeling (see Supplementary Table S1). In addition, we screened the reference lists of identified reviews for relevant literature. We did not restrict our search by date of publication. All references were imported into a literature database using a literature management program (Endnote version X7, Thomson Corp.). First, two authors (A. Gogollari and G. Sroczynski) screened reference titles and abstracts for relevant articles. In a second step, references were selected based on *a priori* inclusion and exclusion criteria (see **Figure 1** legend), after reading the full text document. If there was discrepancy among reviewers, then a third reviewer (L.R. Hallsson) took the decision.

We included decision-analytic modeling studies assessing both the long-term effectiveness and the cost-effectiveness of different early detection and prevention strategies for ovarian cancer reporting patient-relevant outcome measures such as quality-adjusted life-years gained (QALY) or life-years gained (LYG), as well as incremental cost-utility ratios (ICUR; in cost/QALY gained) or incremental cost-effectiveness ratios (ICER; in cost/LYG; ref. 14). We included studies with a time horizon that was sufficiently long (e.g., more than 10 years) to reflect the fact that cancer and preventive interventions affect life expectancy and overall costs (15, 16). We restricted our search to studies from North America and Europe, the countries with highest incidence. We excluded economic studies in languages other than English or German, unsystematic reviews, editorials, letters, abstracts, and studies which were not full health-economic evaluations or evaluating follow-up or treatment strategies, as well as cost studies that did not use a decision-analytic model.

The Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement checklist was applied to all included studies (ref. 17; see Supplementary Table S2). We systematically extracted and summarized in standardized evidence tables the following information: model analytic framework and characteristics (target population, study type, perspective, and time horizon of the analysis, discount rate, model type and simulation type, sensitivity analysis, model validation) as well as effectiveness and cost-effectiveness results of compared strategies. If possible, we calculated ICER and ICUR compared with the next nondominated strategy based on the reported study data, in cases where ICER or ICUR were not reported or compared with no intervention or standard of care in the included study. In addition, to compare cost-effectiveness measures across studies, we calculated ICER or ICUR compared to no intervention or standard of care as a mere descriptive point of reference for all included studies, if data were available. These ICERs or ICURs were visualized in a figure. Evidence tables were stratified by different types of prevention.

To further facilitate comparison across countries and to enable other countries to transfer our results into their currencies, all results were converted to 2017 Euro using the Gross Domestic Product (GDP) Purchasing Power Parities (PPP; available from: https://data.oecd.org/conversion/purchasing-power-parities-ppp.htm) and the Consumer Price Index (CPI; available from: http://stats.oecd.org/index.aspx?DatasetCode=MEI_PRICES) of Europe for inflation. We did not use a specific willingness-to-pay (WTP) threshold for cost-effectiveness, as these vary across different countries (18). In the manuscript text, cost-effectiveness was based on the reported ICER or ICUR compared with the next nondominated effective strategy using the country-specific WTP reported in the included study.

In addition, we used the definition of the World Health Organization (WHO) for cost-effectiveness in our visualization of the results compared to no intervention or standard care. The WHO has recommends thresholds of one to three times the GDP per capita in a specific country (19), thus we show the range using the 2017 GDP per capita in countries of the

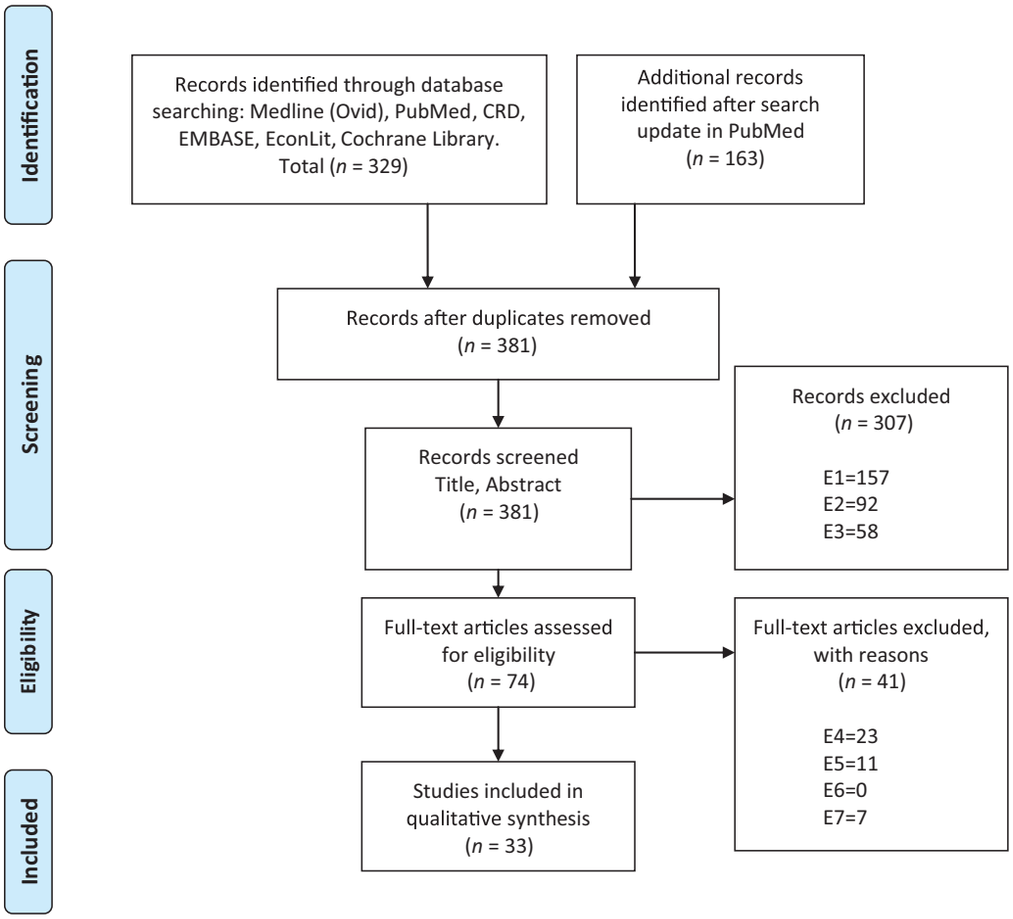

Figure 1.

PRISMA flow diagram: search for cost-effectiveness studies evaluating ovarian cancer screening and/or prevention strategies. Exclusion criteria: E1, other diseases than ovarian cancer or already have ovarian cancer, recurrent cancer or metastases; E2, studies evaluating cost-effectiveness of other interventions (e.g., therapy of ovarian cancer); E3, not decision-analytic modeling studies; E4, not full health-economic studies (cost-effectiveness studies); E5, editorials, reviews, abstracts; E6, not in German or English language; E7, studies from countries other than North America or Europe.

European Union (e.g., that is 32,000 to 95,000 Euros) as an overall point of reference for European countries.

Strategies are considered dominated if they provide less health benefit at higher costs when compared with any other strategy. Therefore, dominated strategies should not be considered by decision makers and no ICER is calculated. Furthermore, extended dominance is applied to eliminate strategies, for which costs and benefits are dominated by a mix of two other alternatives. A dominant strategy provides better health effects at lower cost compared with other strategies (13, 20).

Results

Thirty-three of 389 studies met the inclusion criteria. **Figure 1** shows the PRISMA flow diagram of the literature search and selection.

Included studies were published between 1997 and 2019. The quality of reporting based on the CHEERS checklist varied among the included studies (see Supplementary Table S2). They show heterogeneity regarding target population, study perspective, compliance with intervention, analytic approach, time horizon, discount rate, compared strategies, and mode of prevention (for key characteristics of the included studies, see Supplementary Table S3). The included studies reported health-economic results for the health care systems of the United States of America ($n = 18$), Canada ($n = 4$), United Kingdom ($n = 8$), Norway ($n = 1$), and Germany ($n = 2$).

Included studies were grouped into three main categories based on mode of prevention: (A) ovarian cancer screening ($n = 7$), (B) risk-reducing interventions in women at heterogeneous cancer risk ($n = 17$), and (C) genetic testing followed by risk-reducing interventions for diagnosed mutation carriers ($n = 9$).

In the following paragraphs, the overall health-economic results are summarized for each category and target group presenting ICERs and ICURs compared with the next non-dominated strategy (**Table 1**).

Table 1. Summary of main results of cost-effectiveness studies evaluating (**A**) ovarian cancer screening strategies, (**B**) risk-reducing intervention strategies in women at heterogeneous cancer risk, and (**C**) genetic testing followed by risk-reducing interventions for diagnosed mutation carriers.

Author, year, country, time horizon, discount rate	Population, age range of women (y), ovarian cancer risk	Favored strategy vs. comparator	ICER (in 2017 Euros/LYG)	ICUR (in 2017 Euros/QALY)
(A) Ovarian cancer screening				
Urban, 1997, United States (21), lifetime, 5%[a]	General population, 50–80 y, 2% lifetime risk	Annual CA-125, TVS[b] vs. no screening	854[c]	n.r.
Havrilesky, 2008, United States (26), lifetime, 3%[a]	General population, 50–85 y, 1.42% lifetime risk	Annual screening with HM[d] vs. no screening	69,469	n.r.
	High-risk population, 50–85 y, 10% prevalence of family history of breast and ovarian cancer and relative risk of 2	Annual screening with HM[d] vs. no screening	33,992	n.r.
	High-risk population, 50–85 y, 5% prevalence of family history of breast and ovarian cancer and relative risk of 5	Annual screening with HM[d] vs. no screening	12,534	n.r.
Drescher, 2012, United States (27), lifetime, 3%[a]	General population, 45–85 y, 2% lifetime risk	Annual CA-125, TVS[b] vs. no screening	450[c]	n.r.
Kearns, 2016, UK (25), lifetime, 3.5%[a]	General population, 50–75 y, 2% lifetime risk	Annual MMS vs. no screening	n.r.	9,820
Menon, 2017, UK (24), 25 y, 3.5%[a]	General population, 50–75 y, 2% lifetime risk	Annual MMS vs. no screening	n.r.	59,776
Moss, 2018, UK (23) lifetime, 3%[a]	General population, 50–75 y, 2% lifetime risk	Annual MMS vs. no screening	n.r.	81,373
Naumann, 2018, UK (22), 20 y/30 y, n.r.	General population, 50–70 y, 2% lifetime risk	Annual MMS vs. no screening	439,460[e]	n.r.
	General population, 50–80 y, 2% lifetime risk	Annual MMS vs. no screening	572,987[e]	n.r.
(B) Risk-reducing intervention strategies in women at heterogeneous cancer risk				
BRCA- 1/2 mutation carriers				
Grann, 1998, United States[f] (40), lifetime, 3% [a]	BRCA1 and BRCA2 mutation carriers, ≥30 y, high risk (85% BC risk, 63% OC risk over 40 y)	PBO at 30 y vs. surveillance	Cost-saving	n.r.
	BRCA1 and BRCA2 mutation carriers, ≥30 y, intermediate risk (56% BC risk, 16% OC risk over 40 y)	PBO at 30 y vs. surveillance	Cost-saving	n.r.
	BRCA1 and BRCA2 mutation carriers, ≥30 y, low risk (40% BC risk, 0.06% OC risk over 40 y)	PBO at 30 y vs. surveillance	Cost-saving	n.r.
	BRCA1 and BRCA2 mutation carriers, ≥30 y, high risk (85% BC risk, 63% OC risk over 40 y)	PBO at 30 y + PBM at 30 y vs. surveillance	Cost-saving	n.r.
	BRCA1 and BRCA2 mutation carriers, ≥30 y, intermediate risk (56% BC risk, 16% OC risk over 40 y)	PBO at 30 y + PBM at 30 y vs. surveillance	Cost-saving	n.r.
	BRCA1 and BRCA2 mutation carriers, ≥30 y, low risk (40% BC risk, 0.06% OC risk over 40 y)	PBO at 30 y + PBM at 30 y vs. surveillance	Cost-saving	n.r.
Anderson, 2006, United States[f] (41), lifetime, 3% [g]	BRCA1 mutation carriers, ≥35 y, up to 52% lifetime risk	PBM + PBSO at 35 y vs. PBSO at 35 y	2,469[g]	Dom
	BRCA2 mutation carriers, ≥35 y, up to 23% lifetime risk	PBM at 35 y + PBSO at 35 y vs. PBSO at 35 y	105[g]	2,395[g]
Norum, 2008, Norway[f] (36), lifetime, 3% [a]	BRCA mutation carriers, ≥30 y, up to 58% lifetime risk (Payer's perspective)	PBSO at 35 y vs. no intervention	2,010	n.r.
		PBM at 30 y + PBSO at 35 y vs. PBSO at 35 y	2,509	n.r.
	BRCA mutation carriers, ≥30 y, up to 58% lifetime risk (Societal perspective)	PBM at 30 y +PBSO at 35 y vs. no intervention	570	n.r.
Grann, 2011, United States[f] (39), lifetime, 3% [a]	BRCA1 mutation carriers, 30–65 y, up to 40% lifetime risk	PBM + PBO at 35 y	Cost-saving	-
		PBO at 35 y vs. PBM + PBO at 35 y	Dom	1,537
	BRCA2 mutation carriers, 30–65 y, up to 14% lifetime risk	PBM + PBO at 35 y	Cost-saving	
		PBO at 35 y vs. PBM + PBO at 35 y	Dom	4,038
Kwon, 2013, Canada[f] (38), lifetime, 3% [a]	BRCA1 mutation carriers, ≥40 y, up to 40% lifetime risk	PBSO at 40 y	Cost-saving	-
		PBS at 40 y vs. PBSO at 40 y	Dom	12,957
		PBS at 40 y + PBO at 50 y vs. PBS at 40 y	Dom	24,482
	BRCA2 mutation carriers, ≥40 y, up to 18% lifetime risk	PBSO at 40 y	Cost-saving	-
		PBS at 40 y vs. PBSO at 40 y	Dom	16,596
		PBS at 40 y + PBO at 50 y vs. PBS at 40 y	Dom	58,673

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Table 1. Summary of main results of cost-effectiveness studies evaluating (**A**) ovarian cancer screening strategies, (**B**) risk-reducing intervention strategies in women at heterogeneous cancer risk, and (**C**) genetic testing followed by risk-reducing interventions for diagnosed mutation carriers. (Cont'd)

Author, year, country, time horizon, discount rate	Population, age range of women (y), ovarian cancer risk	Favored strategy vs. comparator	ICER (in 2017 Euros/LYG)	ICUR (in 2017 Euros/QALY)
Müller, 2018, Germany[f] (37), lifetime, 3% [a]	BRCA1 and BRCA2 mutation carriers, ≥30 y, up to 40% lifetime risk	PBM + PBSO at 30 y	Cost-saving	Cost-saving
Women with Lynch syndrome				
Kwon, 2008, United States[h] (44), lifetime, 3% [a]	Lynch syndrome patients, ≥30 y, 10% lifetime risk	Hysterectomy + PBSO at 30 y vs. no prevention	2,385	Ext dom
		Hysterectomy + PBSO at 40 y vs. no prevention	Dom	11,145
Yang, 2011, United States[h] (43), lifetime, 3% [a]	Lynch Syndrome patients, ≥30 y, up to 12% lifetime risk	Hysterectomy + PBSO at 30 y vs. annual gynecologic examination+ TVS+ CA-125, EB	n.r.	Cost-saving
Women with different cancer risk profiles				
Manchanda, 2015, UK (28), lifetime, 3.5% [a]	Postmenopausal women, ≥50 y, 10% lifetime risk	PBSO at 50 y vs. no PBSO	2,139	2,139
	Postmenopausal women, ≥50 y, 8% lifetime risk	PBSO at 50 y vs. no PBSO	4,946	5,121
	Postmenopausal women, ≥50 y, 6% lifetime risk	PBSO at 50 y vs. no PBSO	9,706	11,559
	Postmenopausal women, ≥50 y, 5% lifetime risk	PBSO at 50 y vs. no PBSO	13,376	18,393
	Postmenopausal women, ≥50 y, 4% lifetime risk	PBSO at 50 y vs. no PBSO	19,224	29,342
	Postmenopausal women, ≥50 y, 2% lifetime risk	PBSO at 50 y vs. no PBSO	48,220	770,725
Manchanda, 2016, UK (29), lifetime, 3.5% [a]	Premenopausal women, ≥40 y, 10% lifetime risk	PBSO at 40 y vs. no PBSO	6,723	5,826
	Premenopausal women, ≥40 y, 8% lifetime risk	PBSO at 40 y vs. no PBSO	9,689	10,173
	Premenopausal women, ≥40 y, 6% lifetime risk	PBSO at 40 y vs. no PBSO	14,516	11,612
	Premenopausal women, ≥40 y, 5% lifetime risk	PBSO at 40 y vs. no PBSO	18,136	16,665
	Premenopausal women, ≥40 y, 4% lifetime risk	PBSO at 40 y vs. no PBSO	23,720	22,301
	Premenopausal women, ≥40 y, 2% lifetime risk	PBSO at 40 y vs. no PBSO	48,285	52,675
Kwon, 2015, Canada (33), lifetime, 3% [a]	Premenopausal women undergoing hysterectomy for benign gynecologic conditions at age 35 y, 1.4% lifetime risk	Hysterectomy with PBS vs. hysterectomy alone	Cost-saving	n.r.
	Premenopausal women undergoing tubal ligation for sterilization, at 35 y, 1.4% lifetime risk	PBS vs. tubal ligation	11,683	n.r.
Cadish, 2017, United States (35), n.r., n.r.	Women undergoing vaginal hysterectomy for benign gynecologic conditions regardless of age, 1.3% lifetime risk	Hysterectomy plus PBS vs. hysterectomy alone	Cost-saving	n.r.
Dilley, 2017, United States (34), n.r., 3% [a]	Women undergoing laparoscopic tubal ligation for permanent contraception, at 35 y, 1.3% lifetime risk	PBS vs. tubal ligation	n.r.	17,751
	Women undergoing laparoscopic hysterectomy for benign indications, at 45 y, 1.3% lifetime risk	Hysterectomy plus PBS vs. hysterectomy alone	n.r.	Cost-saving
Tai, 2017, United States (32), lifetime, 3%[a]	Women undergoing a laparoscopic sterilization, at 40 y, 1.5% lifetime risk	PBS vs. tubal clips	4,732	10,887
	Women undergoing a laparoscopic sterilization, at 40 y, 1.5% lifetime risk	PBS vs. tubal coagulation	3,819	7,355
Venkatesh, 2019, United States (31), lifetime, 3% [a]	Pregnant women undergoing cesarean delivery who ask for permanent sterilization, at 35 y, 1.28% lifetime risk	PBS vs. tubal ligation	n.r.	16,575
Bos, 2011, United States[f] (30), lifetime, 3% [a]	Obese women (high fat intake with >36.8% of energy from fat at baseline), ≤50 y, 2% lifetime risk (Societal perspective)	Low fat diet vs. regular diet	n.r.	12,275
	Obese women at high risk for breast cancer (fat intake with ≥32% of energy from fat at baseline), ≤50 y, 2% lifetime risk (Societal perspective)	Low fat diet vs. regular diet	n.r.	14,427
	Obese women (high fat intake with >36.8% of energy from fat at baseline), 50–55 y, 2% lifetime risk (Private health care payer perspective)	Low fat diet vs. regular diet	n.r.	61,848
	Obese women at high risk for breast cancer (fat intake with ≥32% of energy from fat at baseline), 50–55 y, 2% lifetime risk (Private health care payer perspective)	Low fat diet vs. regular diet	n.r.	45,154
	Obese women (high fat intake with >36.8% of energy from fat at baseline), ≥65 y, 2% lifetime risk (Medicare perspective)	Low fat diet vs. regular diet	n.r.	13,375
	Obese women at high risk for breast cancer (fat intake with ≥32% of energy from fat at baseline), ≥65 y, 2% lifetime risk (Medicare perspective)	Low fat diet vs. regular diet	n.r.	14,324

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Table 1. Summary of main results of cost-effectiveness studies evaluating (**A**) ovarian cancer screening strategies, (**B**) risk-reducing intervention strategies in women at heterogeneous cancer risk, and (**C**) genetic testing followed by risk-reducing interventions for diagnosed mutation carriers. (Cont'd)

Author, year, country, time horizon, discount rate	Population, age range of women (y), ovarian cancer risk	Favored strategy vs. comparator	ICER (in 2017 Euros/LYG)	ICUR (in 2017 Euros/QALY)
(C) Genetic testing followed by risk-reducing interventions for diagnosed mutation carriers				
Grann, 1999, United States[f] (47), lifetime, 3% [a]	Ashkenazi Jewish women, age ≥30 y, 14% lifetime risk	GT+ PBM + PBO at 30 y vs. no GT	32,859	n.r.
Rubinstein, 2009, United States (53), lifetime, 3% [a]	Ashkenazi Jewish women, 35–55 y, 14% lifetime risk	GT + PBSO age 35–55 y vs. no GT	9,727	7,832
Manchanda, 2015, UK[f] (50), lifetime, 3.5% [a]	Ashkenazi Jewish women, ≥30 y, 14% lifetime risk	Population-based GT vs. family history-based GT + PBSO + annual MRI/MG or PBM	n.r.	Cost-saving
Holland, 2009, US[f] (48), lifetime, 3% [a]	Women with an associated family risk for breast and/or ovarian cancer, ≥35 y, > 20% lifetime risk	GT+ PBM at 35 y and/or PBSO at 35 y vs. no GT, no prophylactic surgery	n.r.	8,740
Manchanda, 2017, UK[f] (51), lifetime, 3.5% [a]	UK women having two Ashkenazi Jewish grandparents, ≥30 y, 14% lifetime risk	Population-based GT vs. family history-based GT + PBSO + PBM	n.r.	Cost-saving
	U.S. women having two Ashkenazi Jewish grandparents, ≥30 y, 14% lifetime risk	Population-based GT vs. family history-based GT + PBSO + PBM	n.r.	Cost-saving
	UK women having one Ashkenazi Jewish grandparents, ≥30 y, 14% lifetime risk	Population-based GT vs. family history-based GT + PBSO + PBM	n.r.	716
	U.S. women having one Ashkenazi Jewish grandparents, ≥30 y, 14% lifetime risk	Population-based GT vs. family history-based GT + PBSO + PBM	n.r.	Cost-saving
Patel, 2018, UK[f] (52), lifetime, 3.5% [a]	UK Sephardi Jewish women, ≥30 y, 14% lifetime risk	Population-based GT vs. family history-based GT + PBSO + PBM	n.r.	51
	U.S. Sephardi Jewish women, ≥30 y, 14% lifetime risk	Population-based GT vs. family history-based GT + PBSO + PBM	n.r.	342
Hoskins, 2019, Canada (49), lifetime, 1.5%[a]	Canadian women, ≥35 y, 50% (BRCA1) and 12% (BRCA2) lifetime risk	Cascade GT + PBSO vs. no GT	n.r.	Cost-saving
Sun, 2019, UK[f] (46), lifetime, 3%[a]	UK female breast cancer patients, 17%–44% lifetime risk (Payer's perspective)	Multi-gene GT of all BC patients vs. family-history based GT+ PBSO (age 46 y) + PBM (age 42 y)	13,412	12,000
	U.S. female BC patients, 17%–44% lifetime risk (Payer's perspective)	Multi-gene GT of all BC patients vs. family-history based GT+ PBSO (age 46 y) + PBM (age 42 y)	62,044	53,714
	UK female BC patients, 17%–44% lifetime risk (Societal perspective)	Multi-gene GT of all BC patients vs. family-history based GT+ PBSO (age 46 yrs) + PBM (age 42 y)	9,259	8,284
	U.S. female BC patients, 17%–44% lifetime risk (Societal perspective)	Multi-gene GT of all BC patients vs. family-history based GT+ PBSO (age 46 y) + PBM (age 42 y)	58,248	50,481
Müller, 2019, Germany (45), lifetime, 3%[a]	German women with an associated family risk for breast and/or ovarian cancer, ≥35 y, > 20% lifetime risk	GT + PBSO+PBM (45%) or PBM (6%), PBSO (42%), surveillance (7%) at age 35 y vs. no GT	22,318	17,027

Note: ICER and ICUR of the favored strategy are presented for each of the included studies.
Abbreviations: BC, breast cancer; Dom, dominated; GT, genetic testing; HM, Hypothetical test; MMS, multimodal screening (with CA-125 and TVS. as a follow-up test); n.r., not reported; OC, ovarian cancer.
[a]Same discount rate for costs and effects.
[b]Conditional on rising or elevated CA-125.
[c]Per detected cancer case.
[d]Hypothetical marker with a sensitivity of 85% and specificity of 95%.
[e]Costs and effects were not discounted.
[f]The model includes breast cancer.
[g]Effects were not discounted.
[h]The model includes endometrial cancer.

Ovarian cancer screening

Table 1(A) summarizes the health-economic results of studies ($n = 7$; refs. 21–27) evaluating different ovarian cancer screening strategies for postmenopausal women from the general population (see Supplementary Table S4 for more details).

The most recent studies ($n = 4$; refs. 22–25) evaluated multimodal screening (MMS) consisting of annual CA-125 screening interpreted by ROCA with subsequent transvaginal ultrasound (TVS) as a second-line test based on ROCA stratification compared with no screening or annual TVS alone as explored in the UKCTOCS trial (22–25). ROCA-based annual MMS in women as of age 50 was reported ($n = 3$; refs. 23–25) to be possibly cost-effective (depending on the cost for ROCA and on the mortality reduction over the long-term) compared with no screening with an ICUR ranging from 9,800 to 81,400 Euros/QALY. In these studies, a mortality reduction due to ROCA-based MMS of 15% and costs for ROCA-based MMS of 66–145 Euros was assumed. On the contrary, Naumann and colleagues (22) reported that annual ROCA-based MMS compared with no screening may not be cost-effective at an ICER of over 500,000 Euros/LYG for a follow-up of 20 years. The authors (22) assumed annual costs for ROCA-based MMS of about 221 Euros and 11% reduction in ovarian cancer mortality. However, this study (22) did not include the costs for follow-up procedures after positive tests and for cancer treatment and discounting of costs and effects was not reported. Thus, these findings may not be directly comparable with the findings of the other three studies (23–25), which included all direct medical costs and discounted effects and costs at annual rates of 1.5% to 3.5%. All four of these modeling studies (22–25) acknowledged considerable uncertainty in the extent of mortality reduction with ROCA-based MMS.

In comparison with MMS, TVS resulted in increased overtreatment (50 false-positive surgeries performed per 10,000 screens in the TVS group compared with 14 per 10,000 screens in the MMS group), higher cost and lower effects in terms of QALY gained, and was therefore dominated by MMS ($n = 2$; refs. 24, 25). TVS alone or elevated or rising CA-125 alone were both dominated by a strategy with TVS conditional on rising CA-125 levels at a fixed cutoff ($n = 1$; ref. 21). TVS conditional on rising CA-125 levels at a fixed cutoff was reported to be cost-effective compared with no intervention ($n = 2$; refs. 21, 27). However, results of these two studies ($n = 2$; refs. 21, 27) are reported as ICERs per detected case of ovarian cancer, and are therefore not directly comparable with the results from the studies (22–26) that reported ICER/ICUR expressed as cost per QALY gained.

One study (26) assessed a hypothetical rather than a specific existing screening test and explored the impact of test characteristics and costs as well as various screening intervals and screening strategies on their potential clinical utility and cost-effectiveness. The authors of this study (26) reported annual screening of women 50–85 years old with a highly performing hypothetical test or test combinations (85% sensitivity, 95% specificity) to be cost-effective compared with no screening. In the base-case analysis, ICERs ranged between 12,500 Euros/LYG and 69,500 Euros/LYG depending on the prevalence of individuals at increased or high risk for ovarian cancer. ICERs were lower at less frequent screening, higher test specificity, and lower test costs. The lifetime positive predictive value of screening postmenopausal women at average risk was 0.55% in this base-case analysis but could be increased to 22% with increasing specificity from 95% to 99.9%. The model predicted an average of greater than one false positive test over a lifetime for every woman screened when the test specificity was 95% (26).

Overall, the cost-effectiveness of ovarian cancer screening in postmenopausal women from the general population was shown to be sensitive to screening-test costs (22–26), screening-test performance characteristics (26, 27), and the screening interval (26, 27). In addition, based on the results of one study, screening in populations at increased risk for developing ovarian cancer may result in improved cost-effectiveness (26).

Risk-reducing intervention strategies in women at heterogeneous cancer risk

Table 1(B) summarizes the health-economic results of studies evaluating different risk-reducing interventions in women at heterogeneous ovarian cancer risk ($n = 17$; refs. 28–44; see Supplementary Table S5 for more details). One study (42) did not report ICER or ICUR and information on costs and effects were not complete to calculate these.

In women with *BRCA* mutations ($n = 7$; refs. 36–42), prophylactic bilateral salpingo-oophorectomy (PBSO) alone or PBSO plus prophylactic bilateral mastectomy (PBM) were reported to be either cost-saving ($n = 5$; refs. 37–41) or cost-effective ($n = 2$; refs. (36, 41) with ICERs below 2,500 Euro per LYG or QALY gained (**Table 1**). These studies also included the risk for developing breast cancer and results are based on these premises. In terms of cancer mortality reduction, PBSO plus PBM was the most effective strategy. When considering quality of life, PBSO alone ($n = 1$; ref. 41) or PBO alone ($n = 1$; ref. 39) at age 35 or PBS at age 40 with delayed oophorectomy at age 50 ($n = 1$; ref. 38) was the most effective and efficient strategy with ICURs below 24,500 for BRCA-1 carrier, if not cost-saving. In BRCA-2 carriers PBSO plus PBM, age 35 years was still the most effective and efficient strategy with an ICUR of 2,400 Euro per QALY in one study (41), and in the other studies PBO alone at 35 years (39) or PBS alone at 40 years (38) were cost-effective at ICURs below 16,600 Euro per QALY. PBS at 40 years with delayed PBO at 50 years achieved an ICUR of 58,700 Euro per QALY in BRCA-2 carriers (Supplementary Table S5; ref. 38). Cost-effectiveness depended on evaluated strategies including age at surgery and whether quality of life reduction for prophylactic surgery was considered in the evaluation.

In women with Lynch syndrome ($n = 2$; refs. 43, 44), prophylactic hysterectomy (PH) and PBSO at age 30 years was reported to be cost-effective compared with no intervention (44). When considering quality of life, PBSO at age 30 years

was dominated by a delayed PH plus PBSO at age 40 with an ICUR of 11,200 Euros/QALY compared with no intervention (ref. 44; **Table 1**). In the other study, PH plus PBSO at age 30 years was cost-saving compared with annual gynecologic examination (43) These studies additionally included the risk for developing endometrial and/or colorectal cancer and results are based on these premises.

Eight studies (28–35) evaluated risk-reducing intervention strategies in women at various risk profiles for developing ovarian cancer. Two studies (28, 29) used a decision tree to assess at which ovarian cancer risk threshold offering PBSO was cost-effective. In 40-year old premenopausal women with a lifetime risk of 12.9% for developing breast cancer, the ICUR for PBSO compared with no PBSO varied depending on the risk for developing ovarian cancer from 5,800 Euros/QALY for women with 10% lifetime risk to 52,700 Euros/QALY for women with 2% lifetime risk for ovarian cancer (ICER range: 6,700–48,300 Euro/LYG; ref. 29). The authors of this study assumed independent of lifetime risk for cancer a median age of 68 years for the onset of ovarian cancer and a median age of 60 for the onset of breast cancer. In postmenopausal women (age 50 years and older) at various risk levels for ovarian cancer, the ICURs for PBSO compared with no PBSO ranged between 2,100 Euros/QALY gained for women with 10% lifetime risk and 770,700 Euros/QALY for women with 2% lifetime risk for ovarian cancer (ICER range: 2,100–48,200 Euro/LYG; ref. 28). Again, the median age at onset for ovarian cancer was assumed to be 68 years, independent of assumed lifetime risk for developing ovarian cancer. Breast cancer development was not considered in this analysis.

In women undergoing hysterectomy for benign gynecologic conditions ($n = 3$; refs. 33–35), opportunistic PBS was reported to be cost-saving compared with hysterectomy alone. In addition, PBS in women undergoing surgical sterilization ($n = 4$; refs. 31–34) was reported to be cost-effective with ICURs ranging from 7,000 to 18,000 Euros/QALY (ICER range: 4,000–12,000 Euros/LYG) compared with surgical sterilization alone.

In obese women aged 50 to 70 years with 2% ovarian cancer risk ($N = 1$, (30)), low-fat diet in comparison to regular diet may be cost-effective with an ICUR ranging from 12,300 to 14,400 Euros/QALY depending on age at intervention and adopted breast cancer risk, when the study was performed from the societal or Medicare perspective (**Table 1**; Supplementary Table S5). However, when the evaluation was performed from the private health care payer perspective, the ICURs increased above 60,000 Euros/QALY compared with regular diet.

Genetic testing followed by risk-reducing interventions for diagnosed mutation carriers

Table 1(C) summarizes the health-economic results of studies evaluating genetic testing for germline mutations followed by risk-reducing interventions in confirmed mutation carriers ($n = 9$; refs. 45–53; see Supplementary Table S6 for more details).

In Ashkenazi Jewish women ($n = 2$; refs. 47, 53) or in populations at increased risk for mutations ($n = 3$; refs. 45, 48, 49), family history–based genetic testing followed by risk-reducing interventions (e.g., PBSO alone or PBSO plus PBM) for diagnosed mutation carriers compared with no genetic testing was either cost-saving ($n = 1$; ref. 49) or cost-effective with ICERs below 32,900 Euros/LYG ($n = 3$; refs. 45, 47, 53) or at 8,700 Euro per QALY ($n = 1$; ref. 48). Population-wide genetic testing for *BRCA* mutations in Ashkenazi or Sephardi Jewish women ($n = 3$; refs. 50–52) followed by PBM and/or PBSO was either cost-saving (50, 51) or very cost-effective (52) with an ICUR below 400 Euro/QALY compared with testing these women based on a strong family history only. In addition, population-based multi-gene genetic testing in women with breast cancer ($n = 1$; ref. 46) followed by PBSO and/or PBM was cost-effective in United Kingdom and United States with ICURs below 12,000 and 54,000 Euro/QALY, respectively.

To facilitate comparison across studies and countries, we summarized health economic results compared with a common baseline sorted by ovarian cancer risk levels and evaluated strategies within each main category in **Figure 2**. However, as decision making should be based on true stepwise incremental cost-effectiveness ratios, the ICERs compared with the common baseline serve only as a comparative descriptor (54).

The cost-effectiveness results of the different ovarian cancer early detection and prevention strategies depended mainly on the overall risk for developing ovarian cancer in the applied target population. Compared with no intervention, the ICERs and ICURs across included studies fell mostly below the threshold of one-time the per capita GDP (potentially highly cost-effective) for risk-reducing interventions in women at increased or high-risk for ovarian cancer. The same was true for genetic testing of women at increased risk for mutations followed by PBSO for diagnosed mutation carriers. MMS compared with no screening in postmenopausal women from the general population achieved ICURs mainly below two to three times the GDP (potentially cost-effective) with significant variations depending mostly on assumptions on mortality reduction and test costs. Age at intervention was also an important factor resulting in higher ICURs for lower ages (e.g., 30 years vs. 40 years). This highlights the importance to evaluate not only mortality reduction and remaining life expectancy but also quality of life.

Discussion

On the basis of our systematic literature review, the cost-effectiveness of ovarian cancer early detection and prevention strategies depends primarily on women's risk for developing ovarian cancer and secondly on the willingness-to-pay threshold of the specific country.

In postmenopausal women from the general population, ovarian cancer screening using ROCA-based MMS may be considered cost-effective depending on the assumptions made

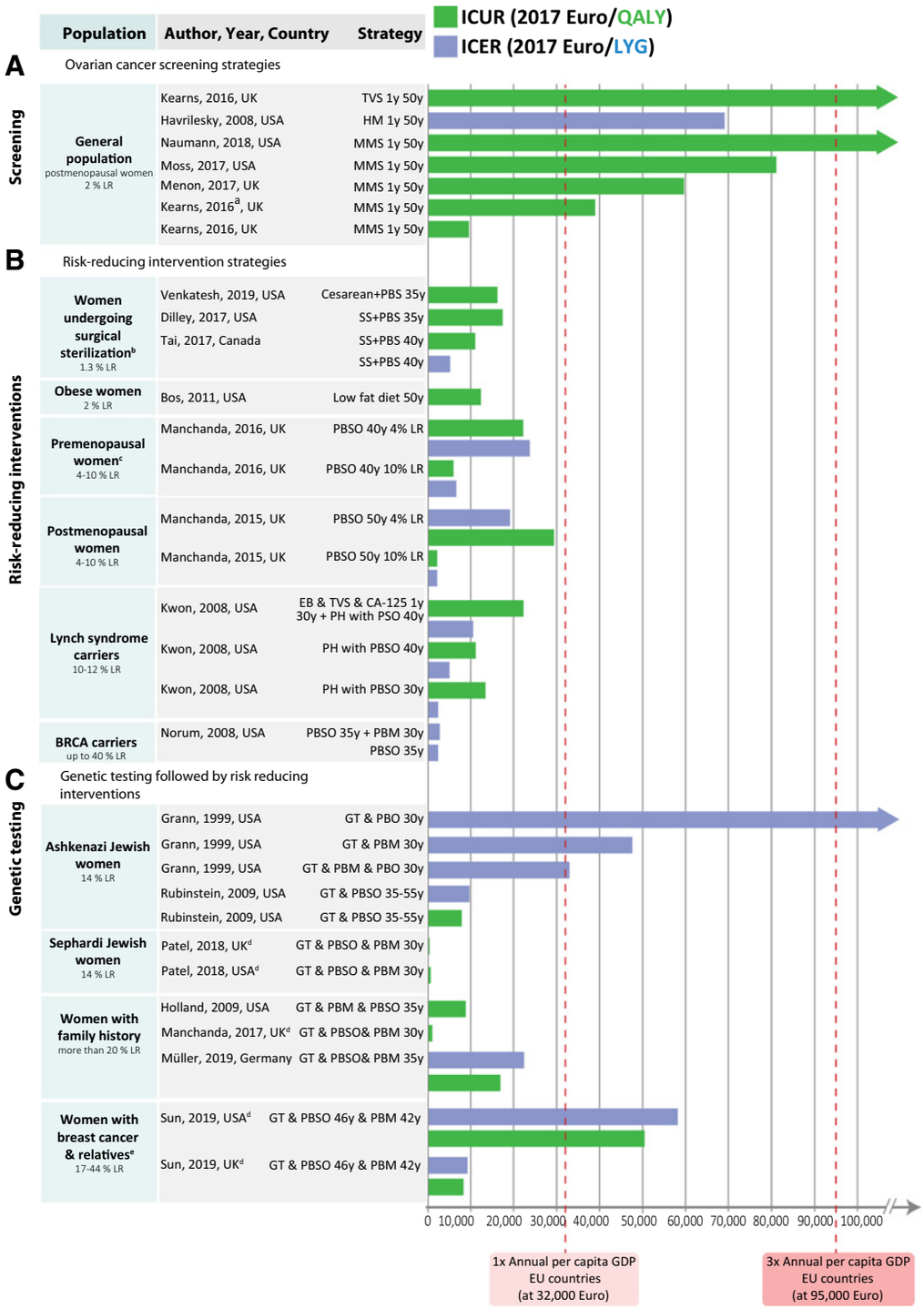

Figure 2.

Health-economic results compared to a common baseline (e.g., standard care) for different target groups. EB, endometrial biopsy; GT, genetic testing; HM, hypothetical marker (Sensitivity: 85%, Specificity: 95%); ICER, incremental cost-effectiveness ratio; ICUR, incremental cost-utility ratio; LYG, life-year gained; LR, lifetime risk; MMS, multimodal screening (CA-125 serum biomarker test followed by transvaginal sonography as a second-line test for patients at increased risk of ovarian cancer); PBS, prophylactic bilateral salpingectomy; PBM, prophylactic bilateral mastectomy; PBO, prophylactic bilateral oophorectomy; PBSO, prophylactic bilateral salpingo-oophorectomy; PH, prophylactic hysterectomy; SS, surgical sterilization; TVS, transvaginal sonography; WTP, willingness-to-pay threshold; y, year. [a]Fitting the same model to all three trial arms using the log-normal distribution. [b]Opportunistic surgery. [c]At increased risk for ovarian cancer and with a lifetime risk of 12.9% for developing breast cancer. [d]The comparator is family history–based genetic testing (state of the art). [e]Subsequent cascade testing of relatives.

regarding the long-term mortality reduction. However, overall results were shown to be sensitive to screening-test costs, screening-test performance characteristics and screening intervals. Thus, further evidence from clinical trials is needed to prove significant long-term mortality reduction. Screening with TVS was less effective, resulted in higher overtreatment and was more costly compared with ROCA-based MMS.

Risk-reducing prophylactic surgery (e.g., PBSO or PBS with delayed oophorectomy) in women at high risk for ovarian cancer (e.g., germline mutation carriers) was considered cost-effective in all included studies. Furthermore, opportunistic risk-reducing surgery (e.g., salpingectomy) in women from the general population undergoing benign hysterectomy or surgical sterilization has been estimated to be a cost-effective prevention strategy.

Genetic testing for mutations associated with an increased risk for ovarian cancer followed by risk-reducing surgery in confirmed mutation carriers was reported to be cost-effective in populations at increased risk for such mutations (e.g., family history of ovarian cancer).

The evaluated studies were conducted in different countries, mostly following their country-specific clinical and health-economic guidelines, which differ across countries and make health-economic comparisons difficult (55).

Variation in clinical practice triggers heterogeneity in the health-economic analyses not only based on different country-specific resource consumptions and costs, but also by including or excluding specific screening or prevention strategies as well as by considering different follow-up pathways. Thus, comparing studies across countries should be taken with care, having in mind that guidelines at baseline or available preventive options might differ across countries which in turn might affect both the effectiveness and the cost-effectiveness results. In the case of an incomplete set of alternative comparator strategies, it is often not possible to base decision making on the truly stepwise incremental cost-effectiveness ratio (56). In these cases, ICERs of included strategies may be biased as the ICER was not drawn to a potentially nondominated strategy that was not included. Consequently, the results of such cost-effectiveness studies may not provide the best possible policy guidance (56).

In addition, the willingness-to-pay threshold indicating cost-effective medical technologies varies across countries with many countries not applying a specific external threshold at all (18). In the United States, for example, a benchmark WTP of 50,000 US$ (approximately 37,500 Euro) per QALY gained is often cited (57), and in the United Kingdom, a threshold of 30,000 UK £ (34,000 Euro) per QALY is established (58). While, the World Health Organization (WHO) in contrast has recommended thresholds of one to three times the GDP per capita (ref. 19; e.g., that is 32,000 to 95,000 Euros for the year 2017 in countries of the European Union).

Potential limitations of the included studies

As in all systematic reviews, the quality of the summary depends strongly on the quality of the included studies. We applied the CHEERS checklist (59) to assess the reporting quality of all included modeling studies and found that not all studies followed this reporting guideline. There are also some aspects of underlying model assumptions and techniques used in the included studies that may have led to potentially biased results.

First, not all studies included quality-of-life measures. In none of the included studies, the anxiety women might experience as a result of a positive test was considered. While in some studies the impact of receiving surgery (either due to true or false positive test results) on quality of life was considered, the impact of receiving a positive test result itself was not incorporated in any of the analyses. Studies not including quality-of-life measures in women receiving a positive test result and/or undergoing surgery might not be able to provide a complete, and therefore valid, assessment of the trade-off between benefits and harms.

Furthermore, false-positive tests leading to unnecessary surgeries (removal of organs) could potentially prevent ovarian cancer in women that were destined to develop ovarian cancer in the future. In modeling studies that are not considering the impact of positive tests and (unnecessary) surgery on quality of life may overestimate the benefits, and therefore, may result in lower cost-effectiveness ratios. Thus, in comparative analyses, screening strategies with lower specificity resulting in more false-positive results and unnecessary surgeries may be falsely favored, when the studies did not thoroughly apply any reduction in quality-of-life for being test-positive or for any kind of treatments or did not consider all necessary costs.

Consideration of quality of life is of high importance, because each strategy might have possible implications for the physiologic and psychologic health of women. An invasive intervention such as the removal of the ovaries especially in women at childbearing age induces artificial menopause and infertility in women. This may result among others in a less favorable body image, changes in the sexual relationship, and psychologic distress (60). Thus, it is not only a highly personal decision of women whether to undergo the recommended mode of prevention, but also a very important and delicate task for qualified clinicians to carefully inform, intensively consult and communicate with women especially when they are at increased risk. Each woman may have individual preferences and may decide on type and time of an intervention based on her individual valuation of benefit-harm trade-offs.

Second, many women at high cancer risk do not wish to undergo prophylactic surgery for a variety of reasons, including concerns about fertility and complications associated with premature menopause. An international survey of *BRCA*-1 and *BRCA*-2 mutation carriers from nine countries revealed that only 57.2% undergo prophylactic surgery (61). However, the impact of compliance was not evaluated in all studies and the applied compliance rates varied significantly across included studies.

Third, in some studies, decision tree models have been used to explore cost-effectiveness across different lifetime risks for

ovarian cancer. Although valuable insights may be derived from those explorative analyses, these results should be interpreted with caution because the decision tree model approach, in general, cannot sufficiently consider the time to event variations and probabilities varying over time. Therefore, decision tree models are mainly applicable to diseases or medical conditions with simple strategies and short analytic time horizons (62). Furthermore, lead-time and overdiagnosis, as well as overtreatment, cannot be considered and explored thoroughly in decision trees. In addition, these studies assumed the same median age at ovarian cancer onset for women independent on the lifetime risk for developing cancer. This assumption may be not valid in real life, as women at increased or high risk for developing cancer may also develop cancer earlier in life. Thus, the median age at cancer onset may be different for women at increased compared with women at low risk for cancer development.

However, the majority of the evaluated studies used state-transition models to assess the effectiveness and cost-effectiveness of different screening and prevention strategies. With this approach, a complex problem with a long time horizon with parameters that might change over time can be handled (13, 16, 62).

Fourth, there was significant variation in the applied discount rates making comparisons of cost-effectiveness ratios across studies difficult. Discounting can be quite influential on the health-economic results. Usually, costs and effects should be discounted at the same rate in health-economic evaluations (63, 64). However, some of the evaluated studies discounted all costs, but not health effects leading to biased cost-effectiveness results. In these cases, the cost-effectiveness ratios are usually lower because the long-term beneficial intervention effects are higher than in discounted analyses.

Fifth, some studies did not include all direct medical costs (e.g., cost for follow-up procedures after positive screening test, cancer treatment costs). Incomplete costs considerations may either lead to overestimated ICERs and ICURs (e.g., cost-savings due to averted cancer treatment cases not considered) or it may lead to underestimation (e.g., additional costs for follow-up procedures not considered). Thus, these studies findings may be biased (65).

Sixth, different approaches for extrapolating trial-based data for cancer-specific mortality were applied, which have a substantial impact on cost-effectiveness results and may also have a potential for bias (66).

Finally, most of the included studies did not completely follow the recommendations for conducting cost-effectiveness analyses (64, 65) and did not perform a second reference case analysis (e.g., analysis based on a societal perspective; ref. 20).

Limitations and strengths of this review

In addition to the limitations of the included studies, there are several limitations of our systematic review itself. We restricted our review to decision-analytic modeling studies evaluating the cost-effectiveness of screening and prevention for ovarian cancer. Furthermore, we searched in relevant electronic databases and screened the references of included studies. It cannot be ruled out that further studies exist in the gray literature. In addition, we limited our search to studies published in English or German language. Studies published in other languages were not assessed. To limit heterogeneity regarding epidemiology, we included only studies from North America and Europe, allowing us to focus on countries with high ovarian cancer incidence. Therefore, our results may not be generalizable to other regions and settings. Furthermore, we visualized the cost-effectiveness results of the included studies compared with no intervention or standard care to allow for mere descriptive comparison across countries. However, it is crucial to highlight that decision making upon cost-effectiveness should be based on true stepwise incremental cost-effectiveness ratios including all essential alternative strategies and comparing them to each other (54). The ICERs compared with the common baseline serve only as a mere comparative descriptor. In addition, we displayed the lower and upper value of the cost-effectiveness threshold based on WHO definition (67) using the 2017 GDP per capita in countries of the European Union. However, each country has its own GDP per capita that should be finally considered. Finally, our summary and critical appraisal is based on the available information given in the included studies, which is not always comprehensive due to limited word counts in scientific journals.

Our findings are consistent with other published reviews on ovarian cancer screening and prevention (9, 68, 69). Two of these published reviews assessed cost-effectiveness studies evaluating ovarian cancer screening and prevention measures (9, 68).

A specific and crucial strength of our review is that we went beyond just reporting published results but used extracted model outputs to perform incremental cost-effectiveness analyses comparing strategies to the next less costly nondominated strategy calculating truly stepwise incremental cost-effectiveness ratios, which are the type of cost-effectiveness measures that are relevant for decision making. To facilitate comparison across studies, all cost data were converted to 2017 Euros. In addition, we presented results compared with a common baseline for comparative descriptive purposes. Substantial differences in these standardized results across studies may help decision makers to further investigate the particular model features and approaches used in these studies. Furthermore, in our review, we focus on risk-adapted screening and prevention strategies and we critically assess modeling aspects. Importantly, we included very recent publications on ovarian cancer screening based on available UKCTOCS trial data, so our results are up-to-date. Finally, a further strength of this review is its methodologic consistency with the PRISMA statement for systematic reviews, and a comprehensive search in most relevant electronic databases was conducted.

Future research

Future ovarian cancer research should focus on developing and investigating effective and cost-effective screening and

prevention approaches tailored to the women's risk. As overall results for MMS based on ROCA are promising, but still uncertain, further evidence from clinical trials is needed to prove significant long-term mortality reduction. Studies, which will use ROCA as a primary screening test to stratify the population into women who benefit from more advanced diagnostics (e.g., cell-free DNA) may be able to close the gap between the onset of ROCA-positivity and visibility of the cancer on imaging. In addition, future research is needed in revealing the evidence for improved risk stratified screening using innovative approaches such as epigenetic testing (e.g., DNA methylation).

Model-based studies may help to preinform empirical studies on different aspects, such as evidence- and consequence-based optimal risk threshold and management algorithms for screening and preventive management based on benefit-harm and cost-effectiveness, and therefore, the selection of the most promising strategies in trials.

With regard to risk-reducing interventions for women at high-risk for ovarian cancer, future research on noninvasive innovative approaches (e.g., risk-reducing medication with low side effects) for reducing the risk for ovarian cancer is needed.

Finally, further health-economic studies are needed evaluating risk-based ovarian cancer screening and prevention approaches. Those studies should consider all relevant health outcomes (e.g., psychological harm and overdiagnosis) and all relevant costs as stated in actual health-economic guidelines (59, 64, 65). Moreover, it is crucial to include all relevant alternative comparator strategies (including all strategies with different screening intervals, start and stop ages, etc.) in the analysis and report all incremental cost-effectiveness ratios of each nondominated strategy compared with its next best nondominated strategy (56). In addition, it is recommended that future health-economic studies consider a second reference case (20) and follow recommendations for standardized reporting of health economic studies (59).

This review may serve as guidance for future research particularly in the field of personalized risk-adapted early detection and prevention of ovarian cancer and may aid health policymakers to make informed decisions regarding resource allocations.

Conclusion

On the basis of our findings, in women at high risk for ovarian cancer, preventive surgery can be considered effective and cost-effective. Genetic testing in populations at increased risk for mutations followed by preventive surgery in diagnosed mutation carriers may be cost-effective. In women from the general population, multimodal screening as of age 50 using a risk-adjusted algorithm may be cost-effective; however, more studies are needed to confirm this finding. In addition, further evidence from clinical trials should be considered to prove a significant mortality benefit. Importantly, the final decision of a woman to receive any of the preventive options relies entirely on her personal circumstances, preferences, and individual benefit-harm tradeoffs. Results of this study could be used to (i) inform health decision and policymakers on the current evidence on cost-effectiveness of ovarian cancer screening and prevention strategies (ii) to develop future health economic models, and finally (iii) to guide decision making in health care toward an optimized and uniform cancer screening and prevention concept in developed countries.

Disclosure of Potential Conflicts of Interest

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References

1. Ferlay J SI, Ervik M, Dikshit R, Eser S, Mathers C, Rebelo M, et al. GLOBOCAN 2012: Estimated cancer incidence, mortality and prevalence worldwide in 2012 v1.0. Lyon, France: IARC.
2. Jayson GC, Kohn EC, Kitchener HC, Ledermann JA. Ovarian cancer. Lancet 2014;384:1376–88.
3. Maringe C, Walters S, Butler J, Coleman MP, Hacker N, Hanna L, et al. Stage at diagnosis and ovarian cancer survival: evidence from the International Cancer Benchmarking Partnership. Gynecol Oncol 2012;127:75–82.
4. Sfakianos GP, Havrilesky LJ. A review of cost-effectiveness studies in ovarian cancer. Cancer Control 2011;18:60–4.
5. Balmana J, Diez O, Rubio IT, Cardoso F. BRCA in breast cancer: ESMO Clinical Practice Guidelines. Ann Oncol 2011;22(Suppl 6): vi31–4.
6. Berek JS, Chalas E, Edelson M, Moore DH, Burke WM, Cliby WA, et al. Prophylactic and risk-reducing bilateral salpingo-oophorectomy: recommendations based on risk of ovarian cancer. Obstet Gynecol 2010;116:733–43.
7. Domchek SM, Friebel TM, Singer CF, Evans DG, Lynch HT, Isaacs C, et al. Association of risk-reducing surgery in BRCA1 or BRCA2 mutation carriers with cancer risk and mortality. JAMA 2010;304: 967–75.
8. US Preventive Services Task Force. Risk assessment, genetic counseling, and genetic testing for BRCA-related cancer: US Preventive Services Task Force Recommendation Statement. JAMA 2019;322: 652–65.
9. Jacobs IJ, Menon U, Ryan A, Gentry-Maharaj A, Burnell M, Kalsi JK, et al. Ovarian cancer screening and mortality in the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS): a randomised controlled trial. Lancet 2016;387:945–56.
10. Kurman RJ, Shih I-M. The origin and pathogenesis of epithelial ovarian cancer: a proposed unifying theory. Am J Surg Pathol 2010;34:433–43.
11. American College of Obstetricians and Gynecologists. Salpingectomy for ovarian cancer prevention. Committee Opinion American College of Obstetricians and Gynecologists. Obstet Gynecol 2015; 620:279–81.
12. Widschwendter M, Jones A, Evans I, Reisel D, Dillner J, Sundstrom K, et al. Epigenome-based cancer risk prediction: rationale, opportunities and challenges. Nat Rev Clin Oncol 2018;15:292–309.
13. Hunink MM, Weinstein MC, Wittenberg E, Drummond MF, Pliskin JS, Wong JB, et al. Decision making in health and medicine: integrating evidence and values. Cambridge, United Kingdom: Cambridge University Press; 2014.
14. Siebert U. When should decision-analytic modeling be used in the economic evaluation of health care? Eur J Health Econom 2003;4: 143–50.
15. Caro JJ, Briggs AH, Siebert U, Kuntz KM. Modeling good research practices–overview: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force–1. Value Health 2012;15:796–803.
16. Siebert U, Alagoz O, Bayoumi AM, Jahn B, Owens DK, Cohen DJ, et al. State-transition modeling: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force–3. Value Health 2012;15:812–20.
17. Husereau D, Drummond M, Petrou S, Carswell C, Moher D, Greenberg D, et al. Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement. Value Health 2013;16:e1–5.
18. Schwarzer R, Rochau U, Saverno K, Jahn B, Bornschein B, Muehlberger N, et al. Systematic overview of cost-effectiveness thresholds in ten countries across four continents. J Comp Eff Res 2015;4:485–504.
19. Report of the Commission on Macroeconomics and Health. Macroeconomics and health: investing in health for economic development. Geneva, Switzerland: World Health Organization. Available from: https://apps.who.int/iris/bitstream/handle/10665/42435/924154550X.pdf;jsessionid=91E933E63E2057AAFF793B0A2F030E48?sequence=1.
20. Neumann PJ, Sanders GD, Russell LB, Siegel JE, Ganiats TG. Cost-effectiveness in health and medicine. Oxford, United Kingdom: Oxford University Press; 2016.
21. Urban N, Drescher C, Etzioni R, Colby C. Use of a stochastic simulation model to identify an efficient protocol for ovarian cancer screening. Control Clin Trials 1997;18:251–70.
22. Naumann RW, Brown J. Ovarian cancer screening with the Risk of Ovarian Cancer Algorithm (ROCA): good, bad, or just expensive? Gynecol Oncol 2018;149:117–20.
23. Moss HA, Berchuck A, Neely ML, Myers ER, Havrilesky LJ. Estimating cost-effectiveness of a multimodal ovarian cancer screening program in the United States: secondary analysis of the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS). JAMA Oncol 2018;4:190–5.
24. Menon U, McGuire AJ, Raikou M, Ryan A, Davies SK, Burnell M, et al. The cost-effectiveness of screening for ovarian cancer: results from the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS). Br J Cancer 2017;117:619–27.
25. Kearns B, Chilcott J, Whyte S, Preston L, Sadler S. Cost-effectiveness of screening for ovarian cancer amongst postmenopausal women: a model-based economic evaluation. BMC Med 2016;14:200.
26. Havrilesky LJ, Sanders GD, Kulasingam S, Myers ER. Reducing ovarian cancer mortality through screening: Is it possible, and can we afford it? Gynecol Oncol 2008;111:179–87.
27. Drescher CW, Hawley S, Thorpe JD, Marticke S, McIntosh M, Gambhir SS, et al. Impact of screening test performance and cost on mortality reduction and cost-effectiveness of multimodal ovarian cancer screening. Cancer Prev Res 2012;5:1015–24.
28. Manchanda R, Legood R, Pearce L, Menon U. Defining the risk threshold for risk reducing salpingo-oophorectomy for ovarian cancer prevention in low risk postmenopausal women. Gynecol Oncol 2015; 139:487–94.
29. Manchanda R, Legood R, Antoniou AC, Gordeev VS, Menon U. Specifying the ovarian cancer risk threshold of 'premenopausal risk-reducing salpingo-oophorectomy' for ovarian cancer prevention: a cost-effectiveness analysis. J Med Genet 2016;53:591–9.
30. Bos AM, Howard BV, Beresford SA, Urban N, Tinker LF, Waters H, et al. Cost-effectiveness analysis of a low-fat diet in the prevention of breast and ovarian cancer. J Am Diet Assoc 2011;111:56–66.
31. Venkatesh KK, Clark LH, Stamilio DM. Cost-effectiveness of opportunistic salpingectomy vs. tubal ligation at the time of cesarean delivery. Am J Obstet Gynecol 2019;220:106.e1–.e10.
32. Tai RWM, Choi SKY, Coyte PC. The Cost-Effectiveness of Salpingectomies for Family Planning in the Prevention of Ovarian Cancer. J Obstet Gynaecol Can 2018;40:317–27.
33. Kwon JS, McAlpine JN, Hanley GE, Finlayson SJ, Cohen T, Miller DM, et al. Costs and benefits of opportunistic salpingectomy as an ovarian cancer prevention strategy. Obstet Gynecol 2015;125:338–45.

34. Dilley SE, Havrilesky LJ, Bakkum-Gamez J, Cohn DE, Michael Straughn J Jr, Caughey AB, et al. Cost-effectiveness of opportunistic salpingectomy for ovarian cancer prevention. Gynecol Oncol 2017; 146:373–9.
35. Cadish LA, Shepherd JP, Barber EL, Ridgeway B. Risks and benefits of opportunistic salpingectomy during vaginal hysterectomy: a decision analysis. Am J Obstet Gynecol 2017;217:603.e1–.e6.
36. Norum J, Hagen AI, Maehle L, Apold J, Burn J, Moller P. Prophylactic bilateral salpingo-oophorectomy (PBSO) with or without prophylactic bilateral mastectomy (PBM) or no intervention in BRCA1 mutation carriers: a cost-effectiveness analysis. Eur J Cancer 2008;44:963–71.
37. Muller D, Danner M, Rhiem K, Stollenwerk B, Engel C, Rasche L, et al. Cost-effectiveness of different strategies to prevent breast and ovarian cancer in German women with a BRCA 1 or 2 mutation. Eur J Health Econ 2018;19:341–53.
38. Kwon JS, Tinker A, Pansegrau G, McAlpine J, Housty M, McCullum M, et al. Prophylactic salpingectomy and delayed oophorectomy as an alternative for BRCA mutation carriers. Obstet Gynecol 2013;121:14–24.
39. Grann VR, Patel PR, Jacobson JS, Warner E, Heitjan DF, Ashby-Thompson M, et al. Comparative effectiveness of screening and prevention strategies among BRCA1/2-affected mutation carriers. Breast Cancer Res Treat 2011;125:837–47.
40. Grann VR, Panageas KS, Whang W, Antman KH, Neugut AI. Decision analysis of prophylactic mastectomy and oophorectomy in BRCA1-positive or BRCA2-positive patients. J Clin Oncol 1998;16:979–85.
41. Anderson K, Jacobson JS, Heitjan DF, Zivin JG, Hershman D, Neugut AI, et al. Cost-effectiveness of preventive strategies for women with a BRCA1 or a BRCA2 mutation. Ann Intern Med 2006;144:397–406.
42. Abdollahian M, Das TK. A MDP model for breast and ovarian cancer intervention strategies for BRCA1/2 mutation carriers. IEEE J Biomed Health Inform 2015;19:720–7.
43. Yang KY, Caughey AB, Little SE, Cheung MK, Chen LM. A cost-effectiveness analysis of prophylactic surgery versus gynecologic surveillance for women from hereditary non-polyposis colorectal cancer (HNPCC) Families. Fam Cancer 2011;10:535–43.
44. Kwon JS, Sun CC, Peterson SK, White KG, Daniels MS, Boyd-Rogers SG, et al. Cost-effectiveness analysis of prevention strategies for gynecologic cancers in Lynch syndrome. Cancer 2008;113:326–35.
45. Müller D, Danner M, Schmutzler R, Engel C, Wassermann K, Stollenwerk B, et al. Economic modeling of risk-adapted screen-and-treat strategies in women at high risk for breast or ovarian cancer. Eur J Health Econ 2019;20:739–50.
46. Sun L, Brentnall A, Patel S, Buist DSM, Bowles EJA, Evans DGR, et al. A cost-effectiveness analysis of multigene testing for all patients with breast cancer. JAMA Oncol 2019;5:1718–30.
47. Grann VR, Whang W, Jacobson JS, Heitjan DF, Antman KH, Neugut AI. Benefits and costs of screening Ashkenazi Jewish women for BRCA1 and BRCA2. J Clin Oncol 1999;17:494–500.
48. Holland ML, Huston A, Noyes K. Cost-effectiveness of testing for breast cancer susceptibility genes (Structured abstract). Value in Health 2009;12:207–16.
49. Hoskins P, Eccleston A, Hurry M, Dyer M. Targeted surgical prevention of epithelial ovarian cancer is cost effective and saves money in BRCA mutation carrying family members of women with epithelial ovarian cancer. A Canadian model. Gynecol Oncol 2019;153:87–91.
50. Manchanda R, Legood R, Burnell M, McGuire A, Raikou M, Loggenberg K, et al. Cost-effectiveness of population screening for BRCA mutations in Ashkenazi jewish women compared with family history-based testing. J Natl Cancer Inst 2015;107:380.
51. Manchanda R, Patel S, Antoniou AC, Levy-Lahad E, Turnbull C, Evans DG, et al. Cost-effectiveness of population based BRCA testing with varying Ashkenazi Jewish ancestry. Am J Obstet Gynecol 2017;217:578.e1–.e12.
52. Patel S, Legood R, Evans DG, Turnbull C, Antoniou AC, Menon U, et al. Cost effectiveness of population based BRCA1 founder mutation testing in Sephardi Jewish women. Am J Obstet Gynecol 2018;218:431.e1–.e12.
53. Rubinstein WS, Jiang H, Dellefave L, Rademaker AW. Cost-effectiveness of population-based BRCA1/2 testing and ovarian cancer prevention for Ashkenazi Jews: a call for dialogue. Genet Med 2009;11: 629–39.
54. Hoch JS, Dewa CS. A clinician's guide to correct cost-effectiveness analysis: think incremental not average. Can J Psychiatry 2008;53: 267–74.
55. Siebert U. Using decision-analytic modelling to transfer international evidence from health technology assessment to the context of the German health care system. GMS Health Technol Assess 2005;1: Doc03.
56. O'Mahony JF, Naber SK, Normand C, Sharp L, O'Leary JJ, de Kok IM. Beware of kinked frontiers: a systematic review of the choice of comparator strategies in cost-effectiveness analyses of human papillomavirus testing in cervical screening. Value Health 2015;18:1138–51.
57. Neumann PJ, Cohen JT, Weinstein MC. Updating cost-effectiveness–the curious resilience of the $50,000-per-QALY threshold. N Engl J Med 2014;371:796–7.
58. Claxton K, Martin S, Soares M, Rice N, Spackman E, Hinde S, et al. Written evidence to the House of Commons Health Select Committee on the NICE cost-effectiveness threshold; 2013. Available from: http://www.publications.parliament.uk/pa/cm201213/cmselect/cmhealth/782/782vw55.htm.
59. Husereau D, Drummond M, Petrou S, Carswell C, Moher D, Greenberg D, et al. Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement. Int J Technol Assess Health Care 2013;29:117–22.
60. van Oostrom I, Meijers-Heijboer H, Lodder LN, Duivenvoorden HJ, van Gool AR, Seynaeve C, et al. Long-term psychological impact of carrying a BRCA1/2 mutation and prophylactic surgery: a 5-year follow-up study. J Clin Oncol 2003;21:3867–74.
61. Metcalfe KA, Birenbaum-Carmeli D, Lubinski J, Gronwald J, Lynch H, Moller P, et al. International variation in rates of uptake of preventive options in BRCA1 and BRCA2 mutation carriers. Int J Cancer 2008; 122:2017–22.
62. Roberts M, Russell LB, Paltiel AD, Chambers M, McEwan P, Krahn M. Conceptualizing a model: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force-2. Med Decis Making 2012;32: 678–89.
63. Attema AE, Brouwer WBF, Claxton K. Discounting in economic evaluations. Pharmacoeconomics 2018;36:745–58.
64. European Network for Health Technology Assessment (EUnetHTA). Methods for health economic evaluations - A guideline based on current practices in Europe; 2015. Available from: https://www.eunethta.eu/wp-content/uploads/2018/03/Methods_for_health_economic_evaluations.pdf.
65. Sanders GD, Neumann PJ, Basu A, Brock DW, Feeny D, Krahn M, et al. Recommendations for conduct, methodological practices, and reporting of cost-effectiveness analyses: second panel on cost-effectiveness in health and medicine. JAMA 2016;316:1093–103.
66. Kuntz KM, Weinstein MC. Life expectancy biases in clinical decision modeling. Med Decis Making 1995;15:158–69.
67. Macroeconomics and health: investing in health for economic development. Report of the Commission on Macroeconomics and Health. Geneva, Switzerland: World Health Organization. Available from: http://apps.who.int/iris/bitstream/10665/42435/1/924154550X.pdf.
68. Kwon JS. Cost-effectiveness of ovarian cancer prevention strategies. Clin Obstet Gynecol 2017;60:780–8.
69. Menon U, Karpinskyj C, Gentry-Maharaj A. Ovarian cancer prevention and screening. Obstet Gynecol 2018;131:909–27.