

A SYSTEMATIC REVIEW ON COST-EFFECTIVENESS STUDIES EVALUATING OVARIAN CANCER EARLY DETECTION AND PREVENTION STRATEGIES

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All authors have completed a unified conflict of Interest declaration form and declare that no company had supported the submitted work. There were no other relationships or activities than those disclosed.

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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 (ICERs) 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 gynecological cancer 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 (USA) 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 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 towards 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 modelling 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). Additionally, 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., Stamford, CT, USA). First, two authors (AG, GS) 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 (LH) 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) (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 (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 to the next non-dominated strategy based on the reported study data, in cases where ICER or ICUR were not reported or compared to no intervention or standard of care in the included study. In addition, in order 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 to the next non-dominated effective strategy using the country-specific WTP reported in the included study.

Additionally, 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 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 to 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 to 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 to the next non-dominated strategy (Table 1).

(A) Ovarian Cancer Screening

Table 1 (A) summarizes the health-economic results of studies (N=7, (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, (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 to 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, (23-25)) to be possibly cost-effective (depending on the cost for ROCA and on the mortality reduction over the long-term) compared to 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 et al. (22) reported that annual ROCA-based MMS compared to 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 to 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 modelling studies (22-25) acknowledged considerable uncertainty in the extent of mortality reduction with ROCA-based MMS.

In comparison to MMS, TVS resulted in increased overtreatment (50 false-positive surgeries performed per 10,000 screens in the TVS group compared to 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, (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 cut-off (N=1, (21)). TVS conditional on rising CA-125 levels at a fixed cut-off was reported to be cost-effective compared to no intervention (N=2, (21,27)). However, results of these two studies (N=2, (21,27)) are reported as ICERs per detected case of ovarian cancer, and are therefore not directly comparable to 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 to 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).

(B) 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, (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 in order to calculate these.

In women with *BRCA* mutations (N=7, (36-42)), prophylactic bilateral salpingo-oophorectomy (PBSO) alone or PBSO plus prophylactic bilateral mastectomy (PBM) were reported to be either cost-saving (N=5, (37-41)) or cost-effective (N=2, ((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, (41)) or PBO alone (N=1, (39)) at age 35 or PBS at age 40 with delayed oophorectomy at age 50 (N=1, (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 35yrs 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 35yrs (39)) or PBS alone at 40yrs were cost-effective at ICURs below 16,600 Euro per QALY. PBS at 40yrs with delayed PBO at 50yrs achieved an ICUR of 58,700 Euro per QALY in BRCA-2 carriers (Supplementary Table S5). 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, (43,44)), prophylactic hysterectomy (PH) and PBSO at age 30 years was reported to be cost-effective compared to 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 to no intervention (44) (Table1). In the other study PH plus PBSO at age 30 years was cost-saving compared to 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 to 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) (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 to 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) (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, (33-35)), opportunistic PBS was reported to be cost-saving compared to hysterectomy alone. In addition, PBS in women undergoing surgical sterilization (N=4, (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 to 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 to regular diet.

(C) 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, (45-53)) (see Supplementary Table S6 for more details).

In Ashkenazi Jewish women (N=2,(47,53)) or in populations at increased risk for mutations (N=3, (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 to no genetic testing was either cost-saving (N=1, (49)) or cost-effective with ICERs below 32,900 Euros/LYG (N=3, (45,47,53)) or at 8,700 Euro per QALY (N=1, (48)). Population-wide genetic testing for *BRCA* mutations in Ashkenazi or Sephardi Jewish women (N=3, (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 to 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, (46)) followed by PBSO and/or PBM was cost-effective in UK and USA with ICURs below 12,000 and 54,000 Euro/QALY, respectively.

To facilitate comparison across studies and countries, we summarized health economic results compared to 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 to 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 to 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 to 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 higher ICURs for lower ages (e.g., 30yrs vs. 40yrs). This highlights the importance to evaluate not only mortality reduction and remaining life expectancy but also quality of life.

DISCUSSION

Based on 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 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 to 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 non-dominated 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 USA, 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 (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 modelling 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, since each strategy might have possible implications for the physiological and psychological 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 psychological 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 to 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) (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. In order 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 to no intervention or standard care in order 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 to 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 non-dominated 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 to 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 methodological 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 pre-inform 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 non-invasive 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 non-dominated strategy compared to its next best non-dominated 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

Based on 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 a) inform health decision and policymakers on the current evidence on cost-effectiveness of ovarian cancer screening and prevention strategies b) to develop future health economic models and finally c) to guide decision making in health care towards an optimized and uniform cancer screening and prevention concept in developed countries.

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DETAILS OF CONTRIBUTORS

Gaby Sroczynski: Project coordinator. Development of study design and research questions. Qualitative analyses and interpretation of results. Results visualization and documentation. Manuscript writing and discussion.

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Nora Pashayan: Discussion and interpretation of results. Manuscript review and discussion.

Martin Widschwendter: FORECEE Principle Investigator. Discussion and interpretation of results. Manuscript review and discussion.

Uwe Siebert: guarantor of this study and the responsible key researcher of the FORECEE project work package. Discussion and interpretation of results. Manuscript review and discussion.

ETHICAL APPROVAL

Ethics approval was not required for this literature review, as no patient-related individual data were used.

TRANSPARENCY DECLARATION

The lead author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported, that no important aspects of the study have been omitted, and that any discrepancies from the study as planned have been explained.

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TABLE

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. Incremental cost-effectiveness ratio (ICER) and incremental cost-utility ratio (ICUR) of the favored strategy are presented for each of the included studies.

| Author, Year, Country, Time Horizon, Discount Rate | Population, Age Range of Women (yrs), Ovarian Cancer Risk | Favored Strategy vs. Comparator | ICER (in 2017 Euro/ LYG) | ICUR (in 2017 Euros/ QALY) |
|--|--|--|--------------------------|----------------------------|
| (A) Ovarian Cancer Screening | | | | |
| Urban, 1997, USA (21), lifetime, 5% ^a | General population, 50 - 80yrs, 2% lifetime risk | Annual CA-125,TVS ^b vs. no screening | 854 ^c | n.r. |
| Havrilesky, 2008, USA (26), lifetime, 3% ^a | General population, 50 - 85yrs, 1.42% lifetime risk | Annual screening with HM ^d vs. no screening | 69,469 | n.r. |
| | High-risk population, 50 - 85yrs, 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 - 85yrs, 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, USA (27), lifetime, 3% ^a | General population, 45 - 85yrs, 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 - 75yrs , 2% lifetime risk | Annual MMS vs. no screening | n.r. | 9,820 |
| Menon, 2017, UK (24), 25 yrs, 3.5% ^a | General population, 50 - 75yrs, 2% lifetime risk | Annual MMS vs. no screening | n.r. | 59,776 |
| Moss, 2018, UK (23) lifetime, 3% ^a | General population, 50 - 75yrs, 2% lifetime risk | Annual MMS vs. no screening | n.r. | 81,373 |
| Naumann, 2018, UK (22), 20yrs /30yrs, n.r. | General population, 50 - 70yrs, 2% lifetime risk | Annual MMS vs. no screening | 439,460 ^e | n.r. |
| | General population, 50 - 80yrs, 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, USA ^f (40), | BRCA1 and BRCA2 mutation carriers, >=30yrs, high risk (85% BC risk, 63% OC risk over 40yrs) | PBO at 30yrs vs. surveillance | Cost-saving | n.r. |

| Author, Year, Country, Time Horizon, Discount Rate | Population, Age Range of Women (yrs), Ovarian Cancer Risk | Favored Strategy vs. Comparator | ICER (in 2017 Euro/ LYG) | ICUR (in 2017 Euros/ QALY) |
|--|---|--|--------------------------|----------------------------|
| lifetime, 3% ^a | BRCA1 and BRCA2 mutation carriers, >=30yrs, intermediate risk (56% BC risk, 16% OC risk over 40yrs) | PBO at 30yrs vs. surveillance | Cost-saving | n.r. |
| | BRCA1 and BRCA2 mutation carriers, >=30yrs, low risk (40% BC risk, 0.06% OC risk over 40yrs) | PBO at 30yrs vs. surveillance | Cost-saving | n.r. |
| | BRCA1 and BRCA2 mutation carriers, >=30yrs, high risk (85% BC risk, 63% OC risk over 40yrs) | PBO at 30yrs + PBM at 30yrs vs. surveillance | Cost-saving | n.r. |
| | BRCA1 and BRCA2 mutation carriers, >=30yrs, intermediate risk (56% BC risk, 16% OC risk over 40yrs) | PBO at 30yrs + PBM at 30yrs vs. surveillance | Cost-saving | n.r. |
| | BRCA1 and BRCA2 mutation carriers, >=30yrs, low risk (40% BC risk, 0.06% OC risk over 40yrs) | PBO at 30yrs + PBM at 30yrs vs. surveillance | Cost-saving | n.r. |
| Anderson, 2006, USA ^f (41), lifetime, 3% ^g | BRCA1 mutation carriers, >=35yrs, up to 52% lifetime risk | PBM + PBSO at 35yrs vs. PBSO at 35yrs | 2,469 ^g | Dom |
| | BRCA2 mutation carriers, >=35yrs, up to 23% lifetime risk | PBM at 35yrs + PBSO at 35yrs vs. PBSO at 35yrs | 105 ^g | 2,395 ^g |
| Norum, 2008, Norway ^f (36), lifetime, 3% ^a | BRCA mutation carriers, >= 30yrs, up to 58% lifetime risk (<i>Payer's perspective</i>) | PBSO at 35yrs vs. no intervention | 2,010 | n.r. |
| | | PBM at 30yrs + PBSO at 35yrs vs. PBSO at 35yrs | 2,509 | n.r. |
| Grann, 2011, USA ^f (39), lifetime, 3% ^a | BRCA1 mutation carriers, 30 - 65yrs, up to 40% lifetime risk | PBM + PBO at 35yrs | Cost-saving | - |
| | | PBO at 35yrs vs. PBM + PBO at 35yrs | Dom | 1,537 |
| | BRCA2 mutation carriers, 30 - 65yrs, up to 14% lifetime risk | PBM + PBO at 35yrs | Cost-saving | - |
| | | PBO at 35yrs vs. PBM + PBO at 35yrs | Dom | 4,038 |
| Kwon, 2013, Canada ^f (38), lifetime, 3% ^a | BRCA1 mutation carriers, >= 40yrs, up to 40% lifetime risk | PBSO at 40yrs | Cost-saving | - |
| | | PBS at 40yrs vs. PBSO at 40yrs | Dom | 12,957 |
| | | PBS at 40yrs + PBO at 50yrs vs. PBS at 40yrs | Dom | 24,482 |
| | BRCA2 mutation carriers, >= 40yrs, up to 18% lifetime risk | PBSO at 40yrs | Cost-saving | - |
| | | PBS at 40yrs vs. PBSO at 40yrs | Dom | 16,596 |
| Müller, 2018, Germany ^f (37), lifetime, 3% ^a | BRCA1 and BRCA2 mutation carriers, >= 30yrs, up to 40% lifetime risk | PBM + PBSO at 30yrs | Cost-saving | Cost-saving |
| Women with Lynch Syndrome | | | | |
| Kwon, 2008, USA ^h (44), lifetime, 3% ^a | Lynch syndrome patients, >= 30yrs, 10% lifetime risk | Hysterectomy + PBSO at 30yrs vs. no prevention | 2,385 | Ext dom |
| | | Hysterectomy + PBSO at 40yrs vs. no prevention | Dom | 11,145 |

| Author, Year, Country, Time Horizon, Discount Rate | Population, Age Range of Women (yrs), Ovarian Cancer Risk | Favored Strategy vs. Comparator | ICER (in 2017 Euro/ LYG) | ICUR (in 2017 Euros/ QALY) |
|--|---|--|--------------------------|----------------------------|
| Yang, 2011, USA ^h (43), lifetime, 3% ^a | Lynch Syndrome patients, >= 30yrs, up to 12% lifetime risk | Hysterectomy + PBSO at 30yrs 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, >= 50yrs, 10% lifetime risk | PBSO at 50yrs vs. no PBSO | 2,139 | 2,139 |
| | Postmenopausal women, >= 50yrs, 8% lifetime risk | PBSO at 50yrs vs. no PBSO | 4,946 | 5,121 |
| | Postmenopausal women, >= 50yrs, 6% lifetime risk | PBSO at 50yrs vs. no PBSO | 9,706 | 11,559 |
| | Postmenopausal women, >= 50yrs, 5% lifetime risk | PBSO at 50yrs vs. no PBSO | 13,376 | 18,393 |
| | Postmenopausal women, >= 50yrs, 4% lifetime risk | PBSO at 50yrs vs. no PBSO | 19,224 | 29,342 |
| | Postmenopausal women, >= 50yrs, 2% lifetime risk | PBSO at 50yrs vs. no PBSO | 48,220 | 770,725 |
| Manchanda, 2016, UK (29), lifetime, 3.5% ^a | Premenopausal women, >= 40yrs, 10% lifetime risk | PBSO at 40yrs vs. no PBSO | 6,723 | 5,826 |
| | Premenopausal women, >= 40yrs, 8% lifetime risk | PBSO at 40yrs vs. no PBSO | 9,689 | 10,173 |
| | Premenopausal women, >= 40yrs, 6% lifetime risk | PBSO at 40yrs vs. no PBSO | 14,516 | 11,612 |
| | Premenopausal women, >= 40yrs, 5% lifetime risk | PBSO at 40yrs vs. no PBSO | 18,136 | 16,665 |
| | Premenopausal women, >= 40yrs, 4% lifetime risk | PBSO at 40yrs vs. no PBSO | 23,720 | 22,301 |
| | Premenopausal women, >= 40yrs, 2% lifetime risk | PBSO at 40yrs vs. no PBSO | 48,285 | 52,675 |
| Kwon, 2015, Canada (33), lifetime, 3% ^a | Premenopausal women undergoing hysterectomy for benign gynecologic conditions at age 35yrs, 1.4% lifetime risk | Hysterectomy with PBS vs. hysterectomy alone | Cost-saving | n.r. |
| | Premenopausal women undergoing tubal ligation for sterilization, at 35yrs, 1.4% lifetime risk | PBS vs. tubal ligation | 11,683 | n.r. |
| Cadish, 2017, USA (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, USA (34), n.r., 3% ^a | Women undergoing laparoscopic tubal ligation for permanent contraception, at 35yrs, 1.3% lifetime risk | PBS vs. tubal ligation | n.r. | 17,751 |
| | Women undergoing laparoscopic hysterectomy for benign indications, at 45yrs, 1.3% lifetime risk | Hysterectomy plus PBS vs. hysterectomy alone | n.r. | Cost-saving |
| Tai, 2017, USA (32), lifetime, 3% ^a | Women undergoing a laparoscopic sterilization, at 40yrs, 1.5% lifetime risk | PBS vs. tubal clips | 4,732 | 10,887 |
| | Women undergoing a laparoscopic sterilization, at 40 yrs, 1.5% lifetime risk | PBS vs. tubal coagulation | 3,819 | 7,355 |
| Venkatesh, 2019, USA (31), lifetime, 3% ^a | Pregnant women undergoing cesarean delivery who ask for permanent sterilization, at 35 yrs, 1.28% lifetime risk | PBS vs. tubal ligation | n.r. | 16,575 |
| Bos, 2011, USA ^f (30), lifetime, 3% ^a | Obese women (high fat intake with >36.8% of energy from fat at baseline), <=50yrs, 2% lifetime risk (<i>Societal perspective</i>) | 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), <=50yrs, 2% lifetime risk (<i>Societal perspective</i>) | Low-fat diet vs. regular diet | n.r. | 14,427 |
| | Obese women (high fat intake with >36.8% of energy from fat at baseline), 50-55yrs, 2% lifetime risk (<i>Private health care payer perspective</i>) | Low-fat diet vs. regular diet | n.r. | 61,848 |
| | Obese women at high risk for breast cancer (fat intake with ≥32% of energy | Low-fat diet vs. regular diet | n.r. | 45,154 |

| Author, Year, Country, Time Horizon, Discount Rate | Population, Age Range of Women (yrs), Ovarian Cancer Risk | Favored Strategy vs. Comparator | ICER (in 2017 Euro/LYG) | ICUR (in 2017 Euros/QALY) |
|--|---|--|-------------------------|---------------------------|
| | from fat at baseline), 50-55yrs, 2% lifetime risk (<i>Private health care payer perspective</i>) | | | |
| | Obese women (high fat intake with >36.8% of energy from fat at baseline), >=65yrs, 2% lifetime risk (<i>Medicare perspective</i>) | 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), >=65yrs, 2% lifetime risk (<i>Medicare perspective</i>) | Low-fat diet vs. regular diet | n.r. | 14,324 |
| (C) Genetic Testing Followed by Risk-Reducing Interventions for Diagnosed Mutation Carriers | | | | |
| Grann, 1999, USA ^f (47), lifetime, 3% ^a | Ashkenazi Jewish women, age ≥30yrs, 14% lifetime risk | GT+ PBM + PBO at 30yrs vs. no GT | 32,859 | n.r. |
| Rubinstein, 2009, USA (53), lifetime, 3% ^a | Ashkenazi Jewish women, 35 - 55yrs, 14% lifetime risk | GT + PBSO age 35-55yrs vs. no GT | 9,727 | 7,832 |
| Manchanda, 2015, UK ^f (50), lifetime, 3.5% ^a | Ashkenazi Jewish women, ≥30yrs, 14% lifetime risk | Population-based GT vs. family history-based GT + PBSO + annual MRI/MG or PBM | n.r. | Cost-saving |
| Holland, 2009, USA ^f (48), lifetime, 3% ^a | Women with an associated family risk for breast and/or ovarian cancer, ≥ 35yrs, > 20% lifetime risk | GT+ PBM at 35yrs and/or PBSO at 35yrs 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, ≥30yrs, 14% lifetime risk | Population-based GT vs. family history-based GT + PBSO + PBM | n.r. | Cost-saving |
| | USA women having two Ashkenazi Jewish grandparents, ≥30yrs, 14% lifetime risk | Population-based GT vs. family history-based GT + PBSO + PBM | n.r. | Cost-saving |
| | UK women having one Ashkenazi Jewish grandparents, ≥30yrs, 14% lifetime risk | Population-based GT vs. family history-based GT + PBSO + PBM | n.r. | 716 |
| | USA women having one Ashkenazi Jewish grandparents, ≥30yrs, 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, ≥30yrs, 14% lifetime risk | Population-based GT vs. family history-based GT + PBSO + PBM | n.r. | 51 |
| | USA Sephardi Jewish women, ≥30yrs, 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, ≥35yrs, 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 (BC) patients, 17% to 44% lifetime risk (<i>Payer's perspective</i>) | Multi-gene GT of all BC patients vs. family-history based GT+ PBSO (age 46yrs) + PBM (age 42yrs) | 13,412 | 12,000 |
| | USA female BC patients, 17% to 44% lifetime risk (<i>Payer's perspective</i>) | Multi-gene GT of all BC patients vs. family-history based GT+ PBSO (age 46yrs) + PBM (age 42yrs) | 62,044 | 53,714 |
| | UK female BC patients, 17% to 44% lifetime risk (<i>Societal perspective</i>) | Multi-gene GT of all BC patients vs. family-history based GT+ PBSO (age 46yrs) + PBM (age 42yrs) | 9,259 | 8,284 |
| | USA female BC patients, 17% to 44% lifetime risk (<i>Societal perspective</i>) | Multi-gene GT of all BC patients vs. family-history based GT+ PBSO (age 46yrs) + PBM (age 42yrs) | 58,248 | 50,481 |

| Author, Year, Country, Time Horizon, Discount Rate | Population, Age Range of Women (yrs), Ovarian Cancer Risk | Favored Strategy vs. Comparator | ICER (in 2017 Euro/LYG) | ICUR (in 2017 Euros/QALY) |
|---|---|---|--------------------------------|----------------------------------|
| Müller, 2019, Germany (45), lifetime, 3% ^a | German women with an associated family risk for breast and/or ovarian cancer, >= 35yrs, > 20% lifetime risk | GT + PBSO+PBM (45%) or PBM (6%), PBSO (42%), surveillance (7%) at age 35yrs vs. no GT | 22,318 | 17,027 |

BC: Breast cancer, Dom: dominated, GT: Genetic testing, HM: Hypothetical test, ICER : Incremental cost-effectiveness ratio, ICUR: Incremental cost-utility ratio, LYG: Life-year gained, MMS: Multimodal screening (with CA-125 and TVS. as a follow-up test), n.r.: Not reported, QALY: Quality-adjusted life year, TVS.: Transvaginal sonography, PBM: Prophylactic bilateral mastectomy, PBO: Prophylactic bilateral oophorectomy, PBS: Prophylactic bilateral salpingectomy, PBSO: Prophylactic bilateral salpingo-oophorectomy, vs.: Versus, yrs: Years.

^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.

FIGURES

Figure 1

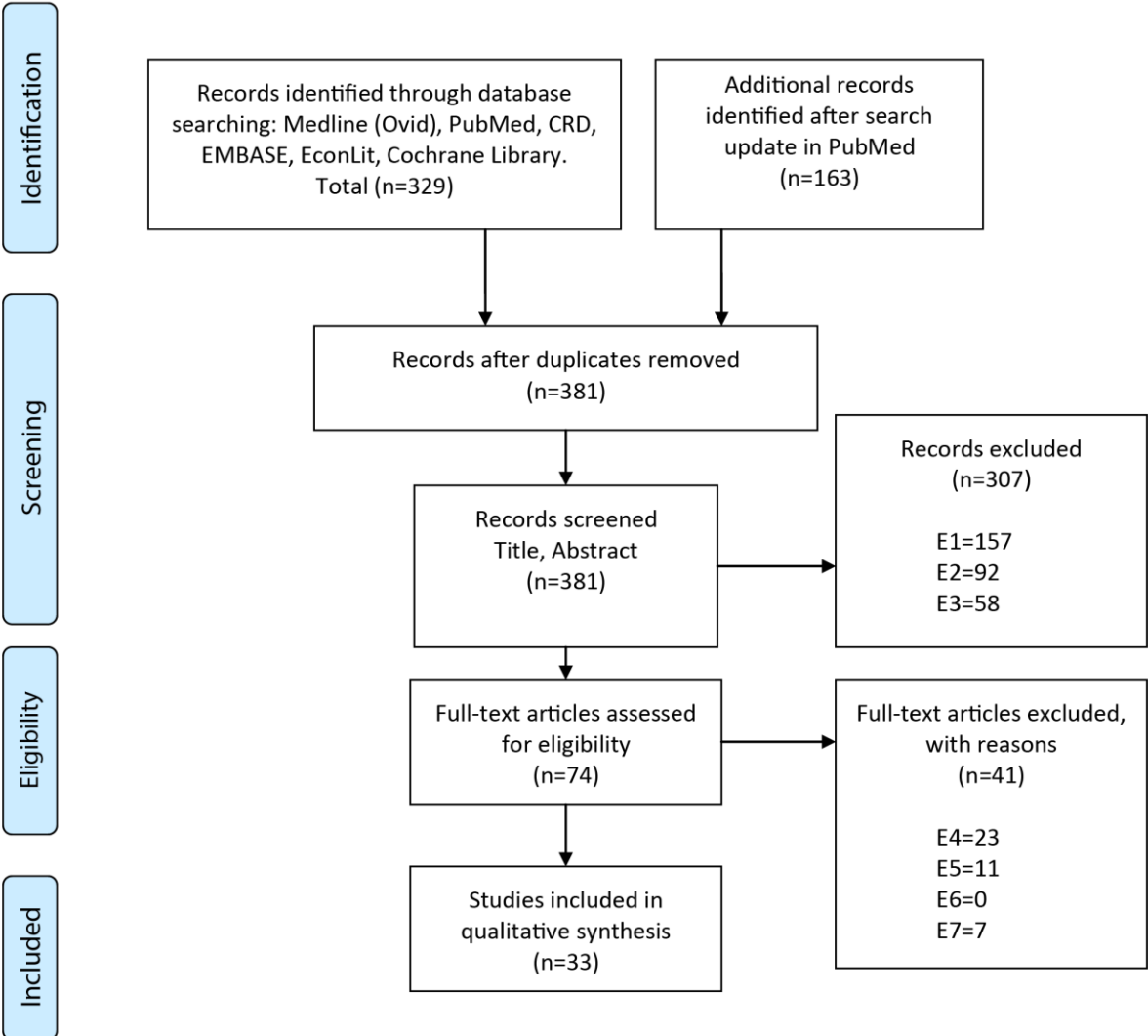


Figure 1. PRISMA flow diagram: search for cost-effectiveness studies evaluating ovarian cancer screening and/or prevention strategies.

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 modelling 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

Figure 2

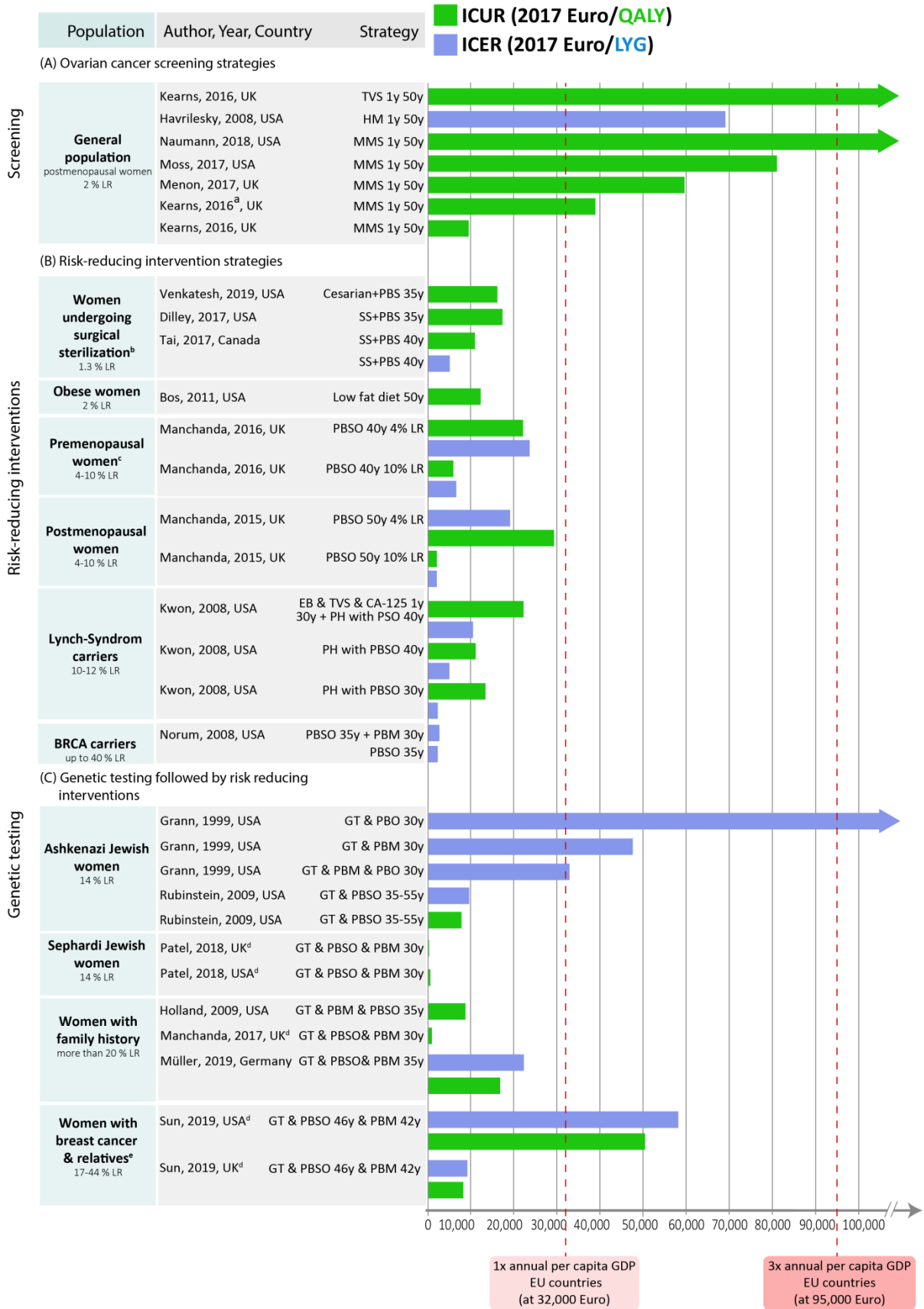


Figure 2. Health economic results compared to a common baseline (e.g., standard care) for different target groups.

EB: Endometrial biopsy, GT: Genetic testing, HM: Hypothetical marker (Sens: 85%, Spec: 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, QALY: Quality-adjusted life year, SS: Surgical sterilization, TVS: Transvaginal sonography, , WTP: Willingness-to-pay threshold, y: Year.

^afitting the same model to all three trial arms using the log-normal; ^bopportunistic surgery; ^cat increased risk for ovarian cancer and with a lifetime risk of 12.9% for developing breast cancer; ^dthe comparator is family-history based genetic testing (state of the art); ^esubsequent cascade testing of relatives.