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Assessing the rates of false-positive ovarian cancer screenings and surgical interventions associated with screening tools: a systematic review

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ABSTRACT

Objective Early detection of ovarian cancer can improve patient outcomes; however, screening tests can yield false-positive results, leading to unnecessary surgical interventions. This systematic review explores the prevalence of false-positive ovarian cancer screenings and subsequent unnecessary surgical interventions.

Methods and analysis Five databases were searched in March 2023 and again in March 2024, encompassing primary literature published between 2003 and 2024. Data collection focused on studies reporting the number of surgical interventions resulting from a false-positive screening result. Studies were categorized by patient risk (average vs high). Studies lacking screening or surgical intervention data, those in which the screening did not directly influence surgical decisions, or those not in English were excluded.

Results Of the 12 papers included, the majority were cohort studies (75%) based in the USA (66%). The primary screening methods included Cancer antigen 125 and transvaginal ultrasound scanning. Patients were stratified by risk, with four studies focused on high-risk populations and eight in average-risk populations. The false-positive and surgical screening rates exhibited significant variability, regardless of risk (0.1%–23.3% and 0%–54.9%, respectively). Complications associated with unnecessary surgical interventions, such as perforation, blood loss and bowel injury, were only reported in four studies. No studies examined the effect these interventions had on patients' quality of life or directly reported the associated costs of these interventions.

Conclusion This review highlights the significant variability in ovarian cancer screening results, which lead to unnecessary and invasive surgical procedures causing complications such as perforation, blood loss and bowel injury.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Early detection of ovarian cancer is crucial; however, screening tests can yield false-positive results and lead to unnecessary surgical interventions. Until screening measures improve, tailoring screening approaches to differentiate between high-risk and average-risk groups can minimise the potential for unnecessary surgery.

WHAT THIS STUDY ADDS

⇒ This study adds to the current literature by exploring the prevalence of ovarian cancer screening false-positive rates and the extent of subsequent unnecessary surgical interventions. It also highlights gaps in our understanding of the impact of false-positive results on quality of life, financial costs and overall well-being.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ These findings emphasise the need for risk stratification in ovarian cancer screenings to reduce the probability of unnecessary surgery.

INTRODUCTION

Ovarian cancer is the fifth-leading cause of cancer-related death among women worldwide.[1] Early detection of ovarian cancer significantly enhances patient outcomes and improves overall survival rates,[2] yet the disease frequently remains undetected until it has reached advanced stages, resulting in a poor 5-year survival rate.[3] This underscores the necessity for efficient screening strategies to identify the disease at an earlier stage, which can markedly improve both treatment results and survival.[4] Nevertheless, the United States Preventive Services Task Force does not recommend specific methods for routine ovarian cancer screening.[5] In the absence of recommended methods, serum tumour biomarkers and imaging techniques such as cancer antige 125 (CA-125) and transvaginal ultrasound (TVUS) have been traditionally used for diagnosing ovarian cancer in symptomatic patients and are also being considered as potential screening tools. However, these methods are prone to producing false-positive results.[6] False-positive screenings can lead to unnecessary surgical interventions, such as bilateral salpingo-oophorectomy causing

patients undue physical, economic and emotional harm.[7] For example, such procedures can result in infertility and induced menopause in premenopausal women.[8] Therefore, given that these tests are the most common means of identifying ovarian cancer, it is essential to explore the potential risks of their use as screening tools.

When considering these tests and others as screening tools, stratifying populations between high-risk and average-risk patient populations is important. Individuals categorised as high risk, often due to genetic factors such as BRCA mutations or a family history of ovarian cancer, face a higher likelihood of developing ovarian cancer. These individuals have a lifetime risk of around 40%, compared with 2.5% in average-risk populations.[9] Given that the incidence of ovarian cancer is higher in this population, there is an emphasis on employing more sensitive screening measures.[10] In these cases, accepting a higher false-positive rate may be a reasonable compromise to ensure early detection and better survival outcomes.[11] However, in the average-risk population, the focus shifts more towards minimising false-positives, as the likelihood of harm from unnecessary interventions may be greater than the benefit of detecting a relatively rare cancer.[12]

This systematic review examines the prevalence of false-positive screenings and the incidence of unnecessary surgical procedures resulting from false-positive tests in ovarian cancer screening studies. It focuses on how risk stratification influences the frequency of these interventions and the subsequent downstream effects they can have on patients. Understanding the current landscape of these screenings is necessary to inform the development of tests that minimise the harmful impacts of false-positive tests while accurately identifying ovarian cancer.

MATERIALS AND METHODS

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. The complete checklist is included in online supplemental appendix.

Search strategy

Eligible studies were initially identified by searching PubMed and Embase in March 2023. To increase the rigour of this study, searches were conducted again in March 2024 using PubMed, Embase, CINAHL and CENTRAL. We also reviewed grey literature using SCOPUS and searched for the last 5 years of conference proceedings from the Ovarian Cancer Research Symposium and the Society of Gynecologic Oncology Annual Meeting. The complete search strategy can be found in online supplemental appendix A.

Selection criteria

All observational studies, retrospective studies and randomised/non-randomised trials published between 2003 and 2023 reporting unnecessary surgical interventions secondary to a false-positive screening were included. Studies published prior to 2003 or not written in English were excluded.

Study selection and data collection process

The studies for this review were selected using Covidence software (figure 1). Two reviewers independently screened all titles and abstracts, blinded to each other's decisions. A study was included if both reviewers independently determined fulfilment of inclusion criteria. Disputes were discussed among reviewers, and, if necessary, resolved by a third reviewer. The same process was followed for full-text review and data extraction.

Data items

The primary outcomes of interest were false-positive rates associated with various ovarian cancer screening tools, as defined by biopsy-proven diagnosis, and the subsequent number of unnecessary surgical interventions. Surgery was considered unnecessary if a positive screening test resulted in a surgical procedure in a patient who was later proven to have benign disease. The secondary outcomes included risk factors associated with false-positive results, complications associated with surgical interventions, financial costs associated with diagnosis and quality of life (QoL). Two reviewers performed data extraction independently, with discrepancies discussed and resolved between the reviewers or, if necessary, by an additional reviewer.

In our analysis, the definition of high-risk versus average-risk populations was based on the criteria set by the studies under consideration. Specifically, individuals in these studies were categorised as high risk for ovarian cancer based on various aspects of their personal or family medical history. These criteria include but were not limited to (a) carrying a BRCA1 or BRCA2 gene mutation; (b) having a personal history of breast cancer; (c) having two close relatives with breast cancer, with at least one diagnosed before age 50 or having bilateral breast cancer; (d) having a direct relative with breast cancer and another with ovarian cancer; (e) having a direct relative diagnosed with both breast and ovarian cancer; (f) having a direct relative with male breast cancer; (g) having two close relatives with ovarian cancer and (h) being of Ashkenazi Jewish descent.[13]

Average-risk populations were those that did not have the study-determined risk factors.

Data analysis

The Newcastle-Ottawa Quality Assessment[14] and RoB 2 form[15] were used to evaluate the risk of bias for the cohort studies and randomised control trials included in this review (online supplemental appendix C). Descriptive statistics were generated with Microsoft Excel.[16]

RESULTS

The search identified 580 articles, and after the abstract and full-text screens, 12 studies were included in the

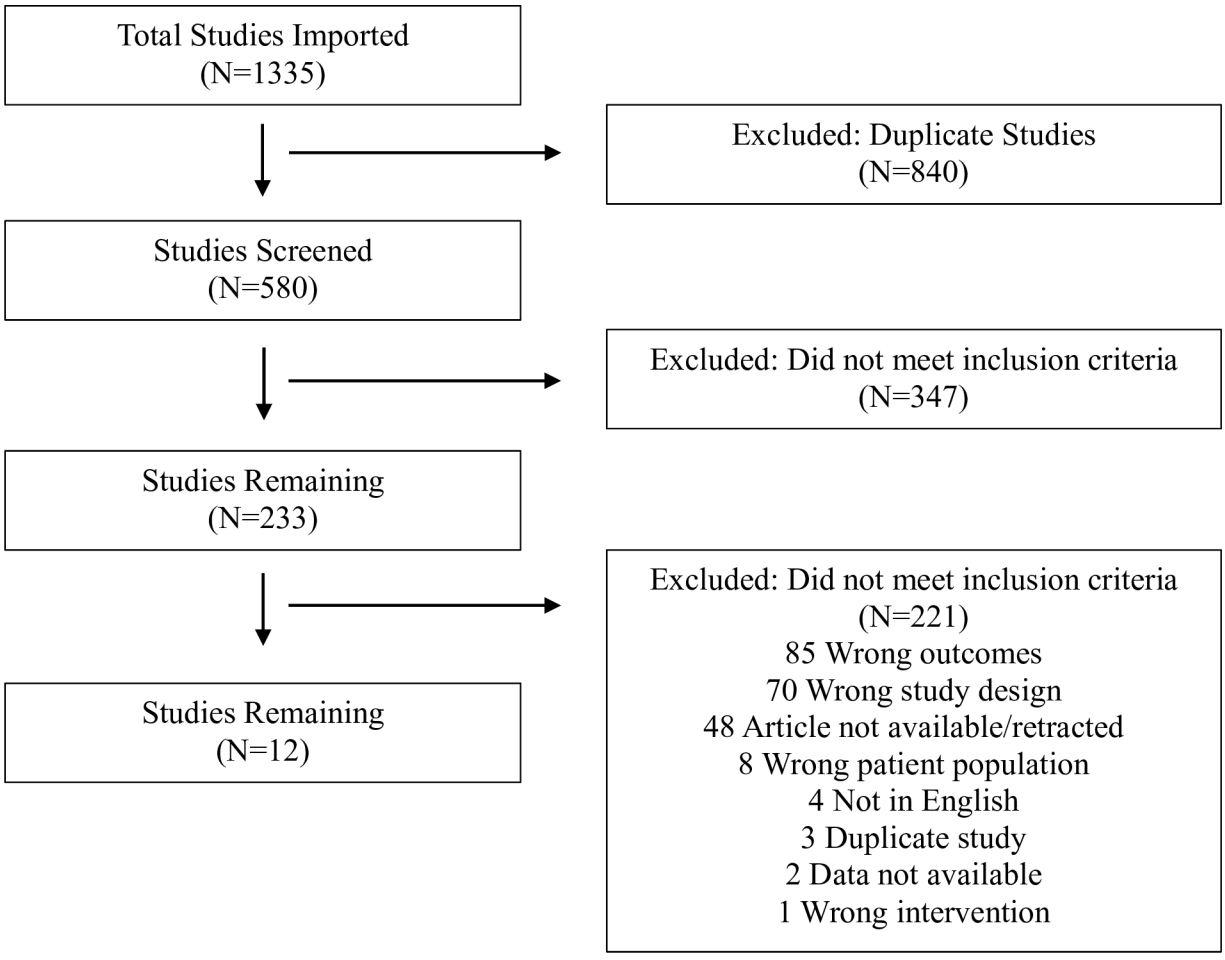

Figure 1 Flow diagram of article review process.

final review (online supplemental appendix table B1). Studies were excluded if they did not report false-positive screening rates and subsequent surgical interventions, were not primary literature, published before 2003, or were not in English. Most studies were cohort studies (75%), and others were randomised control trials (17%) or prospective feasibility studies (8%). Most (66%) of these studies were conducted in the US. The other locations represented were the United Kingdom and the Netherlands (17% each). The median age of participants was 55, ranging from 12 to 95 years old. TVUS and CA-125 were the most commonly assessed screening methods (83% and 67%, respectively). The threshold values for screenings were comparable across the majority of studies (online supplemental appendix table B2). Other methods examined included CT, gynaecological physical exam and a new blood test (Detecting cancers Earlier Through Elective Mutation-based blood Collection and Testing [DETECT-A]) involving multiple blood tests. A notable proportion of the studies investigated combining screening methods (50%). Studies were categorised into two distinct groups based on the population risk profile (average vs high), with 33% of screening studies conducted in high-risk populations and 67% in average-risk populations (table 1).

The four studies that focused on screening high-risk patients had variable false-positive rates (0.1%–23.3%) (table 1). Studies found the highest rates of false-positive tests with TVUS[17 18] while the lowest rates were observed in a study that used CA-125.[19] In one study, a combination of annual gynaecological exams, CA125 and TVUS presented a false-positive rate of 19.30%, leading to a surgery rate of 5.22% (n=20).[20] Others also demonstrated varying levels of false-positive rates, with a false-positive rate of 21.79% for TVUS alone, 10.9% for CA125 alone and 1% combined (TVUS+CA125); surgery rates also varied across these three modalities (9.5%, 4.0% and 1.0%, respectively).[17] Notably, one study assessing high-risk premenopausal and postmenopausal women found higher false-positive rates in premenopausal women (CA-125: 10.8% vs 4.6% and TVUS: 23.3% vs 20.6%); however, the rate of unnecessary surgery across screening tests was lower in premenopausal women compared with postmenopausal women (2.6% vs 4.3%).[18]

Among the eight studies examining average-risk populations, the rates of false-positive results were overall lower (0.2%–7.8%) (table 1). The Prostate, Lung, Colorectal and Ovarian (PLCO) cancer screening trial highlighted a 5% false-positive rate with CA125 and TVUS, corresponding to a surgery rate of 1.38% (n=1080).[21] Another

Table 1 Rate of false-positive test results and unnecessary surgical interventions across studies (n=12).

Reference	Population size	Risk level	Investigation	False-positive rate (%)	Surgery rate N, (%)
Meeuwissen *et al*[20]	383	High	Annual gynaecological exam, CA-125, + TVUS	19.3%	20 (5.2)
Olivier *et al*[17]	312	High	Pelvic exam; CA-125; TVUS; CA-125+TVUS	Pelvic exam: 4.8% CA-125: 10.9% TVUS: 21.8% TVUS+CA-125: 1.0%	Pelvic exam: 15 (2.1) CA125: 34 (4.0) TVUS: 68 (9.5) TVUS+CA-125: 6 (1.0)
Stirling *et al*[19]	1110	High	TVUS; CA-125	Ultrasound: 0.8% CA-125: 0.1%	34 (3.1)
Hensley *et al*[18]	147	High	TVUS; CA-125	CA-125: 10.8% (premenopause) 4.6% (postmenopause) TVUS: 23.3% (premenopause) 20.6% (postmenopause)	Premenopausal: 2 (2.6) Postmenopausal: 3 (4.3) Total: 5 (3.4)
Pavlik *et al*[44]	39337	Average	TVUS	1.2%	472 (1.2)
Ripley-Hager *et al*[45]	444	Average	TVUS	2.2%	13 (2.9)
van Nagell *et al*[24]	71	Average	Ultrasound	6.6%	39 (54.9)
Menon *et al*[25]	202638	Average	CA-125+TVUS	0.2%	827 (0.41)
Nyante *et al*[22]	34253	Average	CA-125+TVUS	3.2%	1125 (3.3)
Buys *et al*[21]	78216	Average	CA-125 + TVUS	5.0%	1080 (1.4)
Croswell *et al*[23]	68436	Average	CA-125; TVUS	CA125: 3.0% TVUS: 7.8%	Minimally invasive procedure: 0 (0.0) 1 (0.0) Moderately invasive procedure 103 (0.4) 677 (2.3) Major surgical procedure 125 (0.4) 874 (3.0)
Lennon *et al*[46]	10006	Average	DETECT-A blood test + PET-CT	0.6%	3 (0.03)

*Positron emission tomography-computed tomography (PET-CT); Cancer antigen 125 (CA-125); Detecting cancers Earlier Through Elective Mutation-based blood Collection and Testing (DETECT-A)
TVUS, transvaginal ultrasound.

study of the same population reported a false-positive rate of 3.20% and a surgery rate of 3.28% (n=1124) using the same modalities.[22] Ultrasound screening in this population resulted in slightly higher rates of false-positive results, with some studies citing rates at 6.6%[19] and 7.8%,[23] leading to unnecessary surgery rates as high as 54% (n=39).[24] However, while the frequency of surgeries was reduced in some cases, the aggregate number of individuals impacted by these interventions was notably higher. This was evident in instances such as two studies where the interventions affected over a thousand people despite surgery rates of only 3%–5% (n=1125 and 1080, respectively).[21 22] Meanwhile the lowest false-positive rate was found in a study using both TVUS and CA-125 (0.2%).[25]

Ancillary factors such as QoL, financial cost, complications and time to diagnosis were also examined. Only four studies reported complications related to unnecessary surgical interventions.[20 21 24 25] Two of these studies, both examining screening in the average-risk population, reported that ~15% of patients had surgical complications.[20 21] In the PLCO study, there were 222 reported complications in patients who underwent surgery without cancer (rate of 15%), of which 40% were infections, 28% were direct surgical complications, 14% were cardiovascular or pulmonary and 18% were other.[21] Common surgical complications included perforation, blood loss, bowel injury and bruising.[21] Importantly, we intended to explore QoL; however, no studies discussed the impact of false-positive results and surgical interventions on QoL.

DISCUSSION

This review emphasises the substantial complexity and variability of false-positive ovarian cancer screenings and unnecessary surgeries. The analysis reveals that while women in the high-risk category are more susceptible to false-positive results, average-risk women exhibit a higher likelihood of undergoing unnecessary surgeries. Furthermore, the lack of discussion in the literature about how unnecessary surgery has impacted the QoL among women highlights a lack of understanding of the potential harms associated with false-positive results. These discrepancies underscore the urgent need for more refined screening strategies that can accurately differentiate between risk levels, aiming to minimise the psychological and physical burden on individuals from interventions that lack a medical necessity.

This systematic review of false-positive ovarian cancer screens and subsequent unnecessary surgical procedures illustrates the need to improve cancer screening. Our review builds on prior research done by Bell *et al*, to demonstrate that, over at least the last three decades, medicine has not greatly improved in preventing false-positive ovarian cancer screens and subsequent unnecessary surgeries for women.[26] This lack of progress highlights a significant challenge for medicine. If we cannot be certain that those who are positively screened have the disease, we risk harming the people we seek to heal. These findings parallel research across different domains of cancer,[27 28] indicating that this issue is not unique to ovarian cancer. Instead, it is a systemic issue that needs to be addressed. In fact, due to this issue, research suggests that clinicians are becoming increasingly hesitant to offer surgery until they are certain that the screening results for that individual are accurate.[29 30]

When applied as screening tools, diagnostic methods like TVUS exhibit variable levels of accuracy, often resulting in higher false-positive rates, especially in high-risk populations. For instance, the diagnostic study using TVUS reported a 1.2% false-positive rate,[31] whereas, in a screening context for high-risk patients, the false-positive rate ranged from 0.78% to 23.3%.[18 19] These results are similar to other studies assessing the use of diagnostic tests for asymptomatic screening.[32 33]

This review highlights the potential benefits of tailoring screening strategies to a patient's risk profile. Combined screening methods resulted in a 19.30% false-positive rate for high-risk individuals.[20] While this led to a surgical intervention rate of 5.22%, the absolute number of individuals affected remains limited due to the smaller number of individuals in this patient population. In contrast, average-risk populations, despite having a lower false-positive rate of 5% in the PLCO cancer screening trial, experienced a higher absolute number of surgeries at a 1.4% rate due to the larger population base, impacting 1125 individuals.[21] Other studies also demonstrate support for risk stratification for ovarian cancer screenings.[34 35] However, risk stratification does raise ethical concerns regarding equitable access to care, privacy and data protection and the psychosocial impacts of informing individuals about their cancer risk.[11] This necessitates a nuanced understanding of the implications of risk stratification in clinical settings, balancing the risk of missed diagnoses with the psychological and physical burdens of false-positives and unwarranted surgeries.

Additionally, the observed variability in false-positive rates across studies could be partly attributed to the inherent limitations of the screening methods. For example, previous studies have shown that the diagnostic accuracy of ultrasound is highly dependent on the operator's experience.[36] Timmerman *et al* analysed the use of ultrasound in the diagnosis of adnexal masses, finding that experienced operators were more accurate (91%) compared with less experienced operators (82%–87%).[36] Similar findings have been observed in other disease sites, where there was notable variation in radiological assessments based on the individual.[36] This highlights the need for involvement of clinicians experienced in the use of ultrasound prior to discussions around surgery, particularly for individuals presenting with clinically ambiguous lesions on initial imaging.

Only four studies reported on the physical consequences of unnecessary surgical interventions. The results from these studies indicate that approximately 15% of individuals experienced complications including perforation, blood loss, bowel injury, fainting and bruising.[20 21 24 25] In the study by Buys *et al*, they found that of the 1080 patients who underwent surgery for a false-positive result, 163 of them experienced major complications.[21] The limited data on complications from ovarian cancer screening highlight a critical gap in understanding the physical impacts on patients. For instance, a study focusing on colorectal cancer screenings found surgery to be the main cause of morbidity and mortality in the colorectal screening programme.[37] To address this, future research must investigate both the immediate and long-term complications, along with their psychological and economic effects. Such a focused investigation may allow for a more balanced evaluation of screening benefits versus risks, informing better healthcare policies and practices.

Finally, no studies directly assessed or commented on the impact of false-positive screenings and/or the subsequent surgical intervention on the patients' QOL or the direct costs of these interventions. Failure to explore these components limits the ability to appraise the risks and benefits of certain screening methods. For example, a study by Wardle *et al*, demonstrated that false-positive results can lead to higher rates of anxiety and depression in patients.[38] These findings stress the need to further assess the psychological, emotional and social consequences of unnecessary surgeries in the context of false-positive screens. Additionally, the economic burden of false-positive results, including unnecessary diagnostic procedures, follow-up tests, surgeries and complications, can significantly inflate healthcare costs, putting financial strain on both patients and the healthcare system.[37] These

findings stress the need to further assess the psychological, emotional, financial and social consequences of unnecessary surgeries in the context of false-positive screens.

These findings underscore the imperative to critically evaluate the clinical utility of ovarian cancer screening tools. Early detection of ovarian cancer has clear advantages; detecting 75% of cancers at stages I or II could halve mortality rates.[2] Yet, there is a notable risk of false-positive results leading to unnecessary surgeries, as indicated by the variability in screening outcomes. This necessitates a re-examination of screening practices in light of Jungner's principles of screening.[39] Such principles stress the importance of a screening test's ability to accurately identify the disease at a treatable stage but also demand that the advantages of screening outweigh any harm.

The evidence suggests that an effective screening strategy in the general population, where ovarian cancer is less prevalent, should aim for a minimum specificity of 99.6% and a sensitivity of 75%–100% to maintain a positive predictive value (PPV) of at least 10%.[40 41] This threshold is imperative to curb the incidence of false-positives, which can lead to significant clinical consequences, including psychological distress, physical harm from unnecessary procedures and the potential misallocation of healthcare resources. However, none of the studies included in this systematic review met these thresholds. Meanwhile, for high-risk groups, the higher lifetime risk in these populations may justify a more aggressive screening approach, as the benefits of early detection could outweigh the risks of false-positives.[13] A screening test with 75% sensitivity and 98% specificity, for instance, would result in a PPV of 13% for this group.[4] Such risk stratification, which has been successfully employed in breast and colorectal cancers, could be instrumental for ovarian cancer as well.[41 42] It could improve detection rates in those most likely to develop the disease and align with the ideal balance of high sensitivity and specificity, minimising harm.

While many advanced methodologies such as multimarker blood assays and imaging techniques have shown increased accuracy over traditional methods, finding the ideal balance to minimise false-positives has remained a challenge.[43] This underscores the importance of continued research and development of more precise diagnostic tools for ovarian cancer. Future research must continue to concentrate on these distinctions, enhancing models to identify high-risk individuals and examining the broader implications of false-positive results. This includes not only the direct complications from unneeded surgeries but also the impact on patients' QoL and overall well-being. Such investigations will contribute to a more intricate understanding of risk versus benefit and the feasibility of tailored screening strategies. This nuanced approach is fundamental to a screening strategy that ensures patients receive the benefits from screening while avoiding the risks of overdiagnosis and overtreatment.

While this study provides meaningful insights into false-positive rates and subsequent unnecessary surgical interventions, several notable limitations exist. First, the retrospective nature of the included studies introduces potential biases and confounding factors. Second, the heterogeneity in study designs and screening methods under investigation may limit the generalisability of our findings. The limited number of studies might also contribute to lack of generalisability. For example, only four studies addressed complications, preventing us from discussing the impact and severity of these complications in depth. Furthermore, excluding non-English studies and those published before 2003 could introduce publication bias. Additionally, a direct correlation between screening and surgical interventions was not always evident, adding complexity to our interpretation of the results.

CONCLUSION

This review underscores the variability in false-positive rates and subsequent surgical interventions in ovarian cancer screening across different risk profiles, emphasising the importance of risk stratification in screening programmes. It draws attention to the need for more targeted research that examines the psychological, financial and physical impacts of false-positive results.

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Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

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