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REVIEW

Gynecologic Cancer Screening and Prevention: State of the Science and Practice

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Opinion Statement

Gynecological cancers, including cervical, endometrial, ovarian, and vulvovaginal cancer, have increasing incidence and mortality globally over the last three decades. In that time, there have been advances in medical therapies and paradigm shifts in surgical treatment which have resulted in a greater quality of life for patients. Clinicians have also refocused efforts to preventing gynecologic cancer. The state of screening and prevention is varied in each of the cancer types. The most comprehensive screening program and only preventable gynecological cancer is cervical cancer, which has been heavily studied since the 1900s. Cervical cytology, primary high-risk human papillomavirus (HPV) testing only, and co-testing are all effective in detecting cervical dysplasia and touted by the major medical. An additional arsenal is prevention through vaccination which has been shown to decrease cervical cancer. Unfortunately, the other gynecological cancers do not have effective screening strategies. The high rates of symptoms in endometrial cancer facilitate detection at an early stage but thus far, asymptomatic screening is only advocated in very high-risk population due to the invasive nature. Novel non-invasive mechanisms are currently under study though none have translated into clinical practice as of yet. Ovarian cancer remains the most innocuous with vague symptoms at onset resulting in late-stage diagnosis. Recommendations for prophylactic oophorectomy only apply to subsets of the population with predisposing genetic mutations. This has led to an ardent push for creative strategies such as opportunistic salpingectomy and a national genetic screening program. These efforts are in addition to the investigations underway researching radiologic, liquid biopsy, and genetic marker screening modalities for all gynecologic cancer. This review article discusses the state of screening, prevention, and recent advancements and pilot studies for each gynecological cancer.

Keywords Gynecological cancer · Screening · Prevention · Cervical cancer · Endometrial cancer · Ovarian cancer

Introduction

From 1990 to 2019, incidence and death rates of ovarian, endometrial, and cervical cancer have greatly increased globally [1]. In the United States, rates of new cancer cases have diverged. The rate of cervical cancer has not changed significantly while there was a notable and significant decrease in the rate of ovarian cancer [2]. Most concerning are the trends in endometrial cancer (EC), which have not only demonstrated a significant increase in incidence but also an increase in mortality [2]. Meanwhile, mortality from cervical cancer and ovarian cancer has decreased from 2.3 to 2.2 deaths and 5.9 to 5.7 deaths per 100,000 people from 2021 to 2022, respectively [2].

The treatment landscape of gynecologic cancer has seen tremendous progress in the past decade. Chemotherapy and radiation have been mainstays of treatment for the past

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50 years. However, in the preceding 10 years, there have been approvals in immunotherapy, targeted therapies, PARP inhibitors, and antibody–drug-conjugates (ADCs) ushering in improvement in oncologic outcomes for persons affected by gynecologic malignancies [3][4–6] [7–9]. Despite new targets to treat advanced disease, the cornerstone of improving outcomes remains primary prevention. With a growing aging population, the need for affordable and accessible screening also increases. This review will appraise the current status of gynecologic cancer screening in the United States.

Cervical Cancer

Cervical cancer (CC) presents in non-specific ways, with symptoms including abnormal vaginal bleeding, pelvic pain, and, in more advanced cases, leg swelling, urinary issues, bowel issues, or hematuria. It can also often present asymptomatically [10–12]. The advent of microscopes in the 1800s and subsequent delineation of abnormal and cancerous cells allowed distinction between benign disease and cancer by Sir Johns Williams in 1886 paved the way for screening [13] [14]. The invention of the colposcope and recognition of the transformation zone by Hans Hinselman gave way to the Papanicolaou smear by George Papanicolaou in 1928 [15]. Since its presentation in 1941, the Pap smear has remained the basis of CC screening to this day [16, 17].

Screening

Current guidelines include three screening options: cytologic testing (i.e. Pap smear and liquid-based cytology), standalone high-risk human papillomavirus (hrHPV) testing, and co-testing which is a combination of the two modalities [18, 19]. HPV is the primary cause of greater than 90% of CC, establishing its integral position in both prevention and screening of CC [20]. HPV infection is transient for many and only a minority of patients will develop resultant severe cervical dysplasia. Previous iterations of CC screening led to overtreatment through colposcopies, biopsies, or excisional treatments such as loop electrocautery excisional procedures (LEEP) or cold knife cone (CKC). In 2018, the screening guidelines were recommended to better delineate persons with a cervix at risk using a threshold of 4.0% or greater of finding cervical intraepithelial neoplasia (CIN) 3 + [21]. The reader is encouraged to review the American Society for Colposcopy and Cervical Pathology (ASCCP) guidelines for full details, but overall, cytology alone screening is recommended for those age 21 to 29. For women aged 30–65, screening could be spaced out every 5 years with either hrHPV testing alone or co-testing or maintained every 3 years with cytology alone [18].

A notable aspect of CC screening is the discordance between governing bodies. The ASCCP recommendations, adopted by both the United States Preventative Task Force (USPTF) and endorsed by the American College of Obstetrics and Gynecology (ACOG), recommends starting screening at age 21 [18, 22]. The American Cancer Society in 2020 raised the threshold from 21 to 25 years old and preferentially recommends primary hrHPV testing over cytology [19]. The rationale of this recommendation is based on hrHPV testing performing nearly the same as co-testing and better than cytology alone while reducing the harm of excessive screening [19, 23, 24]. When analyzing cotesting data from 2003–2015, hrHPV testing was 83.8% positive compared to cytology being 61.9% positive in the diagnosis of CIN3. Only 3.5% of the cotests were positive by cytology and negative for hrHPV, making the argument of non-inferiority of hrHPV testing to cotesting [24]. As further understanding of the carcinogenesis of hrHPV-mediated cancers develop, screening guidelines will continue to be re-examined.

Primary Prevention

There are several unique features of CC. It is the only gynecological cancer with non-surgical primary and secondary prevention options, vaccination and screening respectively. Almost all squamous-cell carcinomas are HPV-associated and approximately 85% adenocarcinomas are HPV-associated [25]. Since the 1950s, incidence and death rates of CC have sharply decreased by 70–75% due to implementation of screening in the U.S. for secondary prevention until primary prevention was introduced with the HPV vaccine in 2006 [26, 27].

At its debut in the aughts, the vaccines were Gardasil (Merck & Co, Rahway, NJ) vaccine (quadrivalent vaccine which protected against HPV-6, −11, −16, −18) and Cervarix (GlaxoSmithKline, Brendford, UK) (bivalent vaccine against HPV-16 and −18) [28, 29]. The Gardasil vaccine then expanded protection for an additional 5 hrHPV types in 2014 and is the only vaccine available in the US after Cervarix was voluntarily taken off the market in 2016 [27, 30, 31]. The vaccine efficacy was evaluated using CIN2 + and CIN3 + as a surrogate for CC. A systematic review found that HPV vaccination reduced the risk of HPV 16/18-associated CIN2/3 + with risk ratios of 0.01 for both in women aged 15–26 at the time of vaccination [32]. There is also moderate evidence that the vaccine also reduces the risk of HPV-associated adenocarcinoma in situ [32].

The vaccine's ability to prevent CC recently emerged. In Sweden, HPV vaccination was successfully implemented with 83.2% national vaccination rate in girls before age 17 and researchers were able to demonstrate a five-fold decrease in incidence of CC in the vaccinated population in large part

due to the national vaccine registry and subsidized costs [33]. This was a landmark trial as the first to prove the positive impact on CC directly. There is also evidence on the impact of not adopting a vaccine program. Japan suspended its recommendation of HPV vaccination in 2013 after highly publicized alleged adverse events of complex regional pain syndrome and inability to walk after receiving the HPV vaccine [34]. This led to a decrease in vaccination rate to less than 1% in females aged 11–16 in 2016 and a subsequent increase in CC incidence nationally [35, 36]. Japan reinstated HPV vaccination recommendations in 2022 but lack of a national HPV vaccine registry created a further barrier to catch-up vaccination [37]. Meanwhile, vaccination in the U.S. is not at goal of > 90% of girls completing the HPV vaccination series by 15, with 54.2% of adolescents between ages 13–17 completing the series [38, 39].

Secondary Prevention

Despite widespread screening programs, CC screening has not been equitably implemented in the U.S. CC is the second leading cause of death in young women (ages 20–39) in the U.S. as of 2019, and stark racial and socioeconomic differences are present in the vaccination and screening of CC [40, 41]. CC incidence is higher in minority populations, including Hispanic women (9.8 per 100,000 women) and Black women (8.7 per 100,000) compared to White women (6.9 per 100,000) between 2017–2021 [42]. There is also a disparity of less CC screening and lower vaccination rates in rural areas compared to urban areas [43]. Differential adherence to screening recommendations suggest a need for better patient outreach, education, and equity.

Looking past vaccination programs and widespread screening, an additional arsenal for CC prevention is the treatment of preinvasive disease encompassing CIN2/3 or carcinoma in situ (CIS). The treatment of cervical dysplasia remains surgical with excisional procedures, which include a CKC or LEEP with cryoablation as an alternative [44]. This approach has numerous setbacks as long-term risks particularly in persons of childbearing age. such as increased risk of preterm delivery where the risk is10.5% and 16.3% in LEEPs and CKCs, respectively [45]. Although excisional procedures are usually successful, 5–16% of women with CIN 2–3 will have recurrence within 5 years of the procedure [46].

Researchers speculate that medical therapy may overcome many of the barriers to surgical therapy, including fertility concerns, cost, equipment, and patient fear [47, 48]. One promising agent was imiquimod, an immune modulator which promotes HPV clearance. A 2024 randomized non-inferiority trial of imiquimod versus excision for recurrent/residual cervical dysplasia was determined futile with regression in only 33% in the imiquimod group compared to 100% of the excision group [49]. Imiquimod failed to demonstrate parity with excisional procedures. Another area of exploration was the use of adjuvant HPV vaccination to reduce recurrent CIN 2/3 lesions. The Vaccin-study was a randomized control trial of 840 women following treatment with LEEP for CIN 2/3 with a primary endpoint of recurrence at 24 months [50]. At the recent International Gynecologic Cancer Society clinical meeting in 2024, the authors reported no difference in CIN2/3 rates with 5.7% versus 8.3% in the vaccine and placebo groups, respectively, which was not significant [51]. There are not currently any non-surgical treatments for cervical dysplasia.

Efforts to further decrease the burden of CC following the advent of HPV vaccine have fallen short. Research remains underway for novel therapeutic approaches, but until that time, we must optimize our current tools by employing regular and equitable screening and promoting vaccination.

Endometrial Cancer

Endometrial cancer (EC), the most common gynecologic malignancy in developed countries, primarily affects postmenopausal patients [52]. Symptoms range from asymptomatic cases to abnormal uterine bleeding (AUB) amongst others [53]. As symptoms prompt further investigation, there is no standardized screening program which is impactful given the prognostic difference in early and late-stage disease. Early-stage EC has a favorable prognosis, with a 5-year survival rate of 80%−90% for stage I disease, which drops to 15%−17% for stage IV [54].

Current Diagnostics

Key risk factors include advanced age, obesity, unopposed estrogen use, polycystic ovary syndrome, and Type 2 Diabetes Mellitus [55]. With a growing elderly population, a rise in obesity and concurrent rise in metabolic disorders such as diabetes, a greater proportion of the population becomes at risk making accurately diagnosing EC vital. Transvaginal ultrasound (TVUS) is a common initial triage tool for postmenopausal bleeding (PMB). An endometrial thickness (ET) of less than or equal to 4 mm has a high negative predictive value (> 99%) [55]. TVUS was previously proposed as a reasonable first approach in early detection; however, this is a source of controversy within the field. In a traditional taxonomy of EC, there are Type I cancers, which are endometrioid grade 1 and 2 histology, and Type II, which include grade 3 endometrioid, clear cell, serous, and other high-risk histologies [53]. Recent data have demonstrated that Type I ECs align more with ET thresholds, while high-risk Type II cancers do not [53, 55, 56]. Additionally, patient characteristics may affect the diagnostic yield of an ultrasound.

Fibroids, present in up to 80% of Black women, can interfere with the measurement of ET [57]. A retrospective diagnostic study by Doll et al. using multicenter data found that the TVUS is not reliable among Black adults at risk for EC [56]. Due to TVUS's low specificity, ACOG highlights a need for additional confirmatory testing with endometrial biopsy (EMB). ACOG guidelines recommend biopsy regardless of ET in cases of persistent PMB and emphasize ET's lack of diagnostic value in premenopausal women. In this population, biopsy decisions depend on symptomology and clinical presentation.

The diagnostic yield of endometrial sampling varies based on technique and indication. Three commonly used sampling methods include EMB with an in-office pipelle, hysteroscopy, and dilation and curettage (D&C). ACOG emphasizes office-based EMB as a minimally invasive, cost-effective first-line tool but this approach risks missing focal lesions. Hysteroscopy allows direct uterine visualization and decreases diagnostic failure due to inadequate sampling, but a 2022 meta-analysis showed no significant difference between EMB and hysteroscopy in rate of detection of EC [58]. A consensus statement of experts in the field emphasized the importance of selecting the diagnostic method based on the clinical context, with hysteroscopy and D&C favored in cases where EMB is non-diagnostic or incomplete.

Emerging Screening Methodologies

Recent research has shifted toward addressing screening challenges. Proposed methods include metabolomic and proteomic profiling of cervicovaginal fluid to identify EC-specific biomarkers. Untargeted metabolomics were used on cervicovaginal lavage samples, analyzing 920 metabolites in patients with EC [59]. Certain lipids, amino acids, and energy metabolism-related metabolites were elevated in EC patients. Tumor characteristics, such as size and myometrial invasion, correlated with specific metabolomic signatures. In a similar vein, proteomic analysis of cervicovaginal fluid and blood plasma were combined with machine learning to elucidate the most diagnostic protein markers in symptomatic postmenopausal women with EC [60]. Distinct protein signatures were identified in EC patients, suggesting potential non-invasive assays for detection, pending larger validation studies. Metabolomic and proteomic profiling are early in their development, and the use of cervicovaginal lavages is unlikely to be incorporated into routine clinical practice without significant advancement.

The use of a tampon as a collection mechanism has shown promise [61]. A self-collection system using vaginal tampons with DNA methylation testing over TVUS to triage patients with AUB has been proposed [62]. In 399 patients, DNA methylation outperformed TVUS in diagnosing EC (area under the curve 0.94 vs. 0.87, respectively) [62]. Cytological analysis of self-collected urine and vaginal samples in women with confirmed EC and unexplained PMB has also been explored [63]. The study distinguished malignant from non-malignant causes of PMB with 90% accuracy. Following these results, the multicenter prospective validation study (NCT03538665) was established to validate the diagnostic accuracy of these samples [64]. The Discovery and Evaluation of Testing for Endometrial and Ovarian Cancer in Tampons (DETECT) study is assessing the performance feasibility, and accessibility of molecular testing for EC detected in paired tampon and tissue specimens [64]. Study completion is anticipated in 2025 and may provide the basis for a less invasive screening mechanism.

Serum biomarkers are also under investigation. Researchers used single-center retrospective data from 300 patients and found that serum cysteine protease inhibitor 1 (CST1) and human epididymis protein 4 (HE4) levels in the EC group were significantly higher compared to other groups. Combined CST1 and HE4 detection showed an AUC of 0.788, with 49.3% sensitivity at 92.5% specificity [65]. At present, the pathway for the positive results from these translation studies to clinical practice remains unclear. There is also growing interest in using plasma-derived biomarkers, including cell-free DNA (cfDNA), circulating tumor DNA (ctDNA), and microRNAs (miRNAs), for detecting EC. Next-generation sequencing of ctDNA with a four-gene panel (CTNNB1, K-ras, PTEN, PIK3CA) detected mutations in > 90% of patients [66]. While many innovations in diagnostic tests are underway, large prospective trials are needed to validate these findings before integrating them into routine clinical practice.

Special Populations

Lynch syndrome (LS), a genetic disorder with pathogenic mutations of the mismatch repair genes. LS confers up to a 60% lifetime EC risk [67]. Up to 10% of patients in whom EC is diagnosed before age 50 have an underlying diagnosis of LS [68]. While only 3% of EC cases are LS-related, early surveillance through cascade testing of family members is critical to identify at-risk family members [67]. The current guidelines in a person with LS recommend EMB every 1–2 years beginning at age 30–35 or earlier if symptomatic, with risk-reducing surgery considered at age 40 [69]. Notably, annual or biennial TVUS have low sensitivity for EC detection in LS [68]. Random EMB every 1–3 years detects hyperplasia or carcinoma in ~ 5% of cases but has not been shown to improve staging or mortality [68]. Current research efforts are aimed at reducing the need for invasive screening and surgical prophylaxis. A panel of methylated DNA markers (MDM) for sporadic colorectal cancers and ECs in patients with LS has been validated [70]. This has led to

a prospective multicenter clinical trial (NCT05410977) to evaluate MDMs for colorectal cancer detection in patients with LS, though we could not identify a comparable trial focused on EC detection.

Another genetic syndrome cohort oftentimes seen in the gynecology population are those with breast cancer genes 1 and 2 (BRCA 1/2). The association between BRCA mutations and EC risk is debated. There is ongoing investigation regarding the potential increased risk of EC, specifically of high-grade histology in BRCA1 mutation carriers [71]. High-grade EC in BRCA1 carriers may stem from tamoxifen use rather than the mutation itself [53]. Current guidelines do not recommend routine hysterectomy for BRCA carriers but advocate shared decision making [72]. Cowden syndrome, a genetic syndrome resulting from a mutation of the phosphotase and tensin homolong (PTEN) gene, increases risk for cancers of the breast, thyroid, and endometrium, with an estimated lifetime risk of 2–28% for EC [73]. Unlike Lynch syndrome, there are no established screening protocols specifically tailored for these patients, creating an unmet need.

Ovarian Cancer

Ovarian cancer (OC) is the leading cause of death among gynecological cancers in the U.S. [74]. Despite its prominence, early detection remains challenging. Patients often present with nonspecific symptoms such as abdominal bloating and indigestion [75]. These symptoms are frequently misattributed to more common conditions like gastrointestinal disorders, leading to delays in diagnosis [76]. As a result, many OC cases are diagnosed at advanced stages, with approximately 75% of cases presenting with stage III/IV disease [77].

Screening and Early Detection

Serum Cancer Antigen 125 (CA-125) has been widely used as a marker as it is a protein marker expressed by epithelial ovarian cells. However, routine screening with fixed cutoffs and TVUS in average-risk women has not demonstrated sufficient sensitivity or specificity to be recommended for asymptomatic women [78–80]. CA-125 is nonspecific as it also expressed in various organs including the peritoneum and the pericardium limiting its utility as a tumor marker in isolation. Furthermore, it is elevated in only 50–60% of women with early-stage OC, while elevated in other benign pelvic pathologies such as endometriosis or pelvic inflammatory disease [81, 82]. Only 20% of elevated CA-125 levels were caused by OC [83]. Serial CA-125 measurement as a screening tool has shown a better positive predictive value (PPV) compared to fixed threshold CA-125 measurements, where the PPV in asymptomatic women at a 35 U/mL cutoff is around 1%, but neither approach has been shown to affect OC mortality [84, 85]. Thus, CA-125 is ill-suited as a screening testing as its high false-positive rate can lead to unnecessary surgeries and psychological distress[84].

TVUS has been widely used to identify and characterize adnexal masses. In 2018, the Ovarian-Adnexal Reporting and Data System (O-RADS) U.S. was introduced as a risk stratification system based on morphologic features for adnexal masses to predict malignancy. O-RADS system classifies adnexal masses into six categories for risk classification from normal to high-risk of malignancy (Table 1). Despite this, imaging cannot differentiate benign from malignant tumors, and small tumors may not be detected early [86]. TVUS as a screening modality has been shown to have a high false-positive rate and low PPV leading to unnecessary surgical intervention [87]. There is no difference in overall survival caused by OC in women who received serial CA-125 and follow-up TVUS, screening TVUS, and no screening at all [87]. USPTF thereby does not recommend TVUS alone or in conjunction with serum CA-125 levels in average-risk patients for routine screening.

To assist clinicians in assessing OC risk, tools such as the Risk of Ovarian Cancer Algorithm (ROCA) have been developed. The ROCA incorporates factors such as age, menopausal status, family history of OC, and serial CA-125 measurements to create a dynamic risk assessment [88]. The Normal Risk Ovarian Screening Study (NROSS) incorporated the ROCA score and CA-125 levels in screening postmenopausal women and with a high-risk score and TVUS was used to further evaluate high-risk women. The PPV in 34/1856 participants was 50% for OC, and this screening reduced incidence of late-stage OC by 34% compared to U.K. Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) controls [89]. Mortality effects were unable to be assessed in the NROSS trial, but further risk stratification in formulating screening guidelines continues to be a work in progress [90].

Another emerging facet of ovarian cancer prevention is opportunistic salpingectomy (OS) in a low-risk population. While there are guidelines for prevention in high-risk populations, such as those with genetic mutations discussed below, there are none for women at average risk. Salpingectomy at the time of hysterectomy has been widely adopted and supported by ACOG and the Society for Gynecology Oncology [91]. Salpingectomy at the time of cesarean delivery in lieu of a partial tubal ligation has also been adopted without a significant rise in complications [92, 93]. This was a foreseeable trajectory as these are performed by Obstetrician/Gynecologists. The innovative approach of risk reduction to has been the championing of OS during non-gynecologic surgeries such as at the time of appendectomy and cholecystectomy [94]. OS at the time of abdominal surgery

Table 1 O-RADS classification according to IOTA lexicon

O-RADS Group	Ultrasound Descriptors	Risk of Malignancy
O-RADS 0	Incomplete evaluation	Not stated
O-RADS 1	Normal premenopausal ovary	0%
O-RADS 2	Classic hemorrhagic cyst ≥ 5 cm to < 10 cm Classic dermoid cyst < 10 cm Classic endometrioma < 10 cm Unilocular smooth cyst ≤ 3 cm Other unilocular smooth cyst ≥ 3 cm to < 10 cm	< 1%
O-RADS 3	Unilocular smooth ≥ 10 cm Unilocular irregular wall Multilocular smooth CS 1–3 < 10 cm Solid smooth CS 1	1% to < 10%
O-RADS 4	Multilocular smooth ≥ 10 cm CS 1–3 Multilocular smooth CS 4 Multilocular irregular Unilocular-solid no papillary projection Unilocular-solid 1–3 papillary projections Multilocular-solid CS 1–2 Solid smooth CS 2–3	10% to < 50%
O-RADS 5	Unilocular-solid with ≥ 4 papillary projections Multilocular-solid CS 3–4 Solid smooth CS 4 Solid irregular Ascites or metastases	50% to 100%

American College of Radiology Ovarian-Adnexal Reporting and Data System (O-RADS) Ultrasound risk stratification and management system. (Reprinted from https://pmc.ncbi.nlm.nih.gov/articles/PMC9955729/table/diagnostics-13–00673-t001/) Ovarian-Adnexal Reporting and Data System Committee, American College of Radiology, with permission according to Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License (https://creativecommons.org/licenses/by/4.0/), including disclaimer in Section 5)

CS Color score

indication-agnostic is likely cost-effective based on models [94, 95]. Implementing this strategy for OS requires buy-in by non-gynecologic surgeons including awareness and technique. As such, educational surgical videos targeting non-gynecologic surgeons have been developed to facilitate uptake of OS [96].

Special Populations: Genetic Risk Factors

The risk of developing OC is 2 to 6 times higher in women with a first-degree relative with OC [97]. In those with a hereditary genetic syndrome such as BRCA 1/2 or LS, a comprehensive clinical screen focusing on individual risk is recommended. Cascade family testing is estimated to miss 50–80% of BRCA1/2 carriers [98]. A U.K.-based study deployed a national genetic testing program for those with Ashekenazi Jewish ancestry and noted effective uptake by the community and detected mutation at anticipated rates [99]. This has translated into a prospective population study with a planned cohort of 5,000 with unknown genetic profile to investigate the benefit and feasibility of universal genetic testing [100]. Identifying more individuals at genetic risk for OC could represent a large-scale primary prevention program.

As we launch efforts to identify at-risk patients, we must contend with the fact there are currently no cost-effective screening strategies for early detection of OC in these high-risk populations [101, 102]. Both CA-125 and TVUS have not been shown to reduce mortality or increase survival in high-risk patients [103]. In all-risk populations, the sensitivity of annual CA-125 testing and ultrasound remains low at 65% and 84.9%, respectively [104, 105]. Retrospective studies show no significant difference in sensitivity and specificity between average-risk and high-risk individuals [106]. For TVUS, sensitivity was 33% and specificity was 85% for both cohorts, while CA-125 yielded a lower sensitivity for high-risk individuals at 50% compared to 66.7% for average risk, with comparable specificity at 83% [106]. Current NCCN guidelines do not recommend routine OC screening with measurement of serum CA-125 level or TVUS in this population [78]. These tests may be used for short-term surveillance and preoperative planning starting twice a year, starting at age 30–35 until the time they choose to

pursue risk-reducing BSO [107]. The most effective risk-reducing strategy is prophylactic BSO, typically recommended after childbearing at age 35–40 in BRCA1 and age 40–45 for BRCA2 carriers, reducing the risk of OC by 80–90% [102, 108]. Studies regarding the oncologic outcome for bilateral salpingectomy with delayed oophorectomy are currently underway in the U.S. and internationally (NCT01907789, NCT02321228).

The lifetime risk of OC in LS is 6.7–12%, compared to 1.39% in the general population [109, 110]. Preventing gynecologic malignancy in this population represents a challenge given the limitations of screening tests in both OC and EC. A hypothetical cohort of LS patients estimated that annual screening with TVUS, EMB, and CA-125 from age 30, followed by prophylactic surgery at age 40, is the most cost-effective prevention strategy [111]. Current NCCN guidelines suggest considering risk-reducing hysterectomy and BSO for risk reduction of both EC and OC after discussion of fertility desires [78]. An analytic model found that surgical management led to the longest expected survival at 79.98 years in women with LS [112]. However, there is no clinical evidence supporting routine OC screening in women with LS, and NCCN does not recommend routine use of CA-125 or TVUS as screening tools for these patients [78, 113].

Liquid Biopsy: Emerging Diagnostic Tool

"Liquid biopsy" is an evolving area of research for OC detection and is positioned as a promising screening tool for early detection of OC. This non-invasive method analyzes ctDNA, RNA, or exosomes in blood samples to detect cancer-associated genetic alterations. ctDNA, derived from primary or metastatic tumors, can be isolated from plasma or serum. It can be used for early diagnosis, monitoring treatment response, and detecting drug resistance, as ctDNA levels correlate with tumor factors such as histology, vascularization, and size [114]. ctDNA has already shown utility in prostate cancer, non-small cell lung cancer, and colon cancer by providing more sensitive measurements compared to conventional serum markers to monitor disease progression [115–118]. A meta-analysis concluded ctDNA was significantly associated with decreased overall survival (hazard ratio (HR) = 2.70; 95% CI [2.02–3.61]) and progression-free survival (HR = 2.51, 95% CI [1.83,3.45]) in patients with OC [114]. Recent studies suggest that "liquid biopsy" may also aid in cancer surveillance, as it may detect biomarkers such as ctDNA before clinical symptoms appear [119, 120]. However, its clinical utility is still under investigation and further studies are needed to validate its role and cost-effectiveness in routine clinical practice for OC [121].

Vulvar and Vaginal Cancer

In the US, primary vulvar and vaginal cancers account for only 6% and up to 2% of gynecological cancers, respectively [122]. Given the low incidence and lack of effective screening methods, there are currently no guidelines for asymptomatic screening for vulvar intraepithelial neoplasia (VIN) or vaginal intraepithelial neoplasia (VaIN). Affected patients are oftentimes identified through clinical symptoms which include itching, pain or changes to the vulvar skin [123]. Biopsy of any suspicious lesions is recommended, as histology is the gold-standard for establishing a diagnosis.

Classification of VIN recently dichotomized to reflect the underlying etiology: differentiated VIN (known as dVIN) is an HPV independent pathway while usual-type VIN (uVIN) is associated with hrHPV [124]. The primary prevention strategy for uVIN and subsequent squamous cell carcinoma (SCC) of the vulva is HPV vaccination to reduce infection. For patients affected by dVIN, routine pelvic examination with a healthcare provider is the best mechanism for detection of early signs.

VaIN is highly associated with hrHPV infection [125]. A positive cervical hrHPV test was shown to have an increased hazard of developing vulvar and vaginal SCC, HR was 3.7 for vulvar SCC and 19.9 for vaginal SCC compared to women with a negative cervical hrHPV test [126]. Regular HPV and/or cytology testing is indicated as screening for vaginal cancer in women with prior hysterectomy for severe dysplasia [127]. Although pelvic examinations have been subject to scrutiny in recent years, pelvic examinations are recommended to prevent the progression of VIN or VaIN to cancer [128].

Conclusion

Preventing gynecologic malignancies present a significant public health challenge. Survival rates vary significantly within gynecological cancers despite improvements in treatment and management across the board. This underscores the need for screening and early detection as which are key to reducing mortality rates. CC screening has established and widely used screening methods that make primary prevention possible, yet it remains a burden and difficult to implement. Early detection of OC and EC remains a challenge due to lack of effective, non-invasive, and reliable screening methods. Emerging research with liquid biopsies with biomarkers, circulating tumor cells, ctDNA, exosomes, and circulating cell-free microRNAs, as well as biomarkers with concomitant use of AI offer hope for more targeted and accurate diagnostic tools. However, much remains to be done to refine and validate these approaches for

clinical application. Nevertheless, the ongoing development of new technologies and biomarkers presents an exciting frontier in gynecological cancer prevention. Until that time, we must rely on the tried-and-true method in practice since the first known physician: the history and physical.

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  ○ This study is of importance because it is an ongoing trial evaluating the performance of a novel, non-invasive endometrial cancer detection tool, self-collected vaginal tampon specimens, that could transform diagnostic pathways for women with postmenopausal bleeding.

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  ○ This study is of importance because it compared long-term mortality in ovarian cancer in patients without screening and different screening modalities, with no significant difference in mortality rates in all groups.

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Data Availability No datasets were generated or analysed during the current study.

Declarations

Conflict of Interest The authors declare no competing interests.

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