Systematic Review

Early Ovarian Cancer Detection in the Age of Fallopian Tube Precursors

A Systematic Review

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OBJECTIVE: To determine biomarkers other than CA 125 that could be used in identifying early-stage ovarian cancer.

DATA SOURCES: Ovid MEDLINE ALL, EMBASE, Web of Science Core Collection, ScienceDirect, Clinicaltrials.gov, and CAB Direct were searched for English-language studies between January 2008 and April 2023 for the concepts of high-grade serous ovarian cancer, testing, and prevention or early diagnosis.

METHODS OF STUDY SELECTION: The 5,523 related articles were uploaded to Covidence. Screening by two independent reviewers of the article abstracts led to the identification of 245 peer-reviewed primary research articles for full-text review. Full-text review by those reviewers led to the identification of 131 peer-reviewed primary research articles used for this review.

TABULATION, INTEGRATION, AND RESULTS Of 131 studies, only 55 reported sensitivity, specificity, or area under the curve (AUC), with 36 of the studies reporting at least one biomarker with a specificity of 80% or greater specificity or 0.9 or greater AUC.

CONCLUSION: These findings suggest that although many types of biomarkers are being tested in ovarian cancer, most have similar or worse detection rates compared with CA 125 and have the same limitations of poor detection rates in early-stage disease. However, 27.5% of articles (36/131) reported biomarkers with better sensitivity and an AUC greater than 0.9 compared with CA 125 alone and deserve further exploration.

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Ovarian cancer is rare with a 1.1% lifetime risk; however, it is the leading cause of death among gynecologic malignancies in the United States. High-grade serous carcinoma is the most common histologic subtype. It is generally accepted that the origin for high-grade serous carcinoma is the fallopian tube epithelium. Although reports dating back to 2001 describe the fallopian tube epithelium as the primary site of origin for high-grade serous carcinoma, it not was until 2007 that the understanding of the origin of high-grade serous carcinomas shifted, as detailed in two reviews.[1,2] More than 75% of patients are diagnosed with stage III or IV disease. Most patients experience no or nonspecific symptoms.[3,4] The frequent late stage of diagnosis is a consequence of limited markers for detection at early stages (I or II).[3,4]

Currently, there are no clinical tests that can reliably detect early-stage ovarian cancer. The data from the UKCTOCS (UK Collaborative Trial of

Ovarian Cancer Screening) study showed that strategies such as CA 125 testing and ultrasonography in the general population stage shifted ovarian cancer diagnosis to earlier stages but did not improve overall survival, highlighting the need to identify biomarkers or modalities for detecting precursor lesions such as serous tubal intraepithelial carcinoma associated with high-grade serous carcinoma.[5] Once an ovarian mass is detected, there are significant limitations in the ability to preoperatively risk-stratify ovarian neoplasms because this would limit patients at low risk to unnecessary surgical procedures.[6,7]

Currently, serum tests such as CA 125 or MUC16 and human epididymis protein 4 are used to assist with preoperative ovarian neoplasm risk stratification. CA 125 is a glycoprotein, and human epididymis protein 4 is a broad protease inhibitor. Both are detected in serum of patients with ovarian cancer; however, neither CA 125 nor human epididymis protein 4 alone has adequate sensitivity or specificity to detect early stages of the disease.[8] The American College of Obstetricians and Gynecologists recommends referral to a gynecologic oncologist in patients with adnexal masses and a CA 125 of 35 units/mL in postmenopausal patients and 200 units/mL in premenopausal patients.[9] The sensitivity and specificity of CA 125 are better in postmenopausal patients at 88.7% and 98.1% compared with 64.0% and 94.1%, respectively, in premenopausal patients.[10] Confounding ovarian cancer detection, CA 125 may be elevated for reasons unrelated to malignancy such as endometriosis, menstruation, physiologic states, pregnancy, or anything that would irritate the peritoneal lining, thus decreasing its sensitivity.[8]

Human epididymis protein 4 is commonly overexpressed in epithelium-derived ovarian tumors. In a meta-analysis by Wang et al,[11] human epididymis protein 4 and CA 125 had similar abilities to discriminate malignancy from benign mass with an area under the curve (AUC) of 0.89 for human epididymis protein 4 and 0.87 for CA 125. Human epididymis protein 4 had a higher specificity than CA 125, especially in the premenopausal subgroup (93.8 vs 76.3, respectively), whereas CA 125 performed better in the postmenopausal group compared with human epididymis protein 4.[11] Although human epididymis protein 4 shows potential improvement in premenopausal patients as a single marker, the overall similar detection rate in the general population, high cost of the test, and limited availability in certain areas limit its use.[12]

Given the limitations of any single marker, both human epididymis protein 4 and CA 125 have been evaluated in combination to evaluate risk of malignancy. For example, human epididymis protein 4 and CA 125 are used in the ROMA (Risk of Ovarian Malignancy Algorithm),[13] which is a numerical score used to predict risk of epithelial ovarian cancer in patients with an adnexal mass. In a meta-analysis, ROMA performed similarly to CA 125, with a sensitivity between 76% and 86%, whereas the specificity was between 74% and 95%. The AUC for the ROMA algorithm was better than for human epididymis protein 4 or CA 125 alone at 0.93 compared with 0.82 and 0.88, respectively.[14] The Risk of Malignancy Index is another risk assessment tool that is referenced that uses menopausal status, ultrasound findings, and CA 125 levels. A Risk of Malignancy Index score higher than 200 proved to be a good predictive model for classifying a patient with an adnexal mass as high risk for malignancy with a sensitivity of 87.5%, specificity of 90.7%, and AUC of 0.9.[15]

With the limitations in current biomarker testing, the need for a better marker remains a challenge. The goal of this systematic review is to explore the recent literature for promising tests that could aid in the detection of ovarian cancer, particularly in the setting of early-stage disease and precursor lesions, for which there is a paucity of effective testing.

SOURCES

Search terms and criteria for each of the five repositories queried are detailed in Appendix 1, available online at http://links.lww.com/AOG/D543. Five repositories were queried to complete a comprehensive search and to avoid missing relevant articles. Clinicaltrials.gov was independently queried. Eligibility criteria of literature were determined a priori. Included studies had to include information about high-grade serous ovarian cancer and meet one of the following criteria: identifies a biomarker or method that correlates or associates with diagnosis of disease, identifies a biomarker or method that correlates or associates with early-stage disease, identifies a biomarker or method that correlates or associates with the diagnosis of early-stage disease, identifies a biomarker or method that correlates or associates with disease progression, or identifies a biomarker or method that correlates or associates with the transformation of fallopian tube epithelium. Exclusion criteria of publications included prior systematic reviews or reviews of the literature reporting biomarkers or detection methods, articles in languages other than English, articles published before 2008, and articles that discuss high-grade serous carcinoma but identify a biomarker or method that correlates or associates solely to therapy response,

neoadjuvant response, therapy resistance, or prognostication.

A comprehensive literature search was designed and performed by a medical librarian (C.P.) in January 2022 for the concepts of high-grade serous ovarian cancer, testing, and prevention or early diagnosis. Relevant publications were identified by searching the following databases with a combination of standardized index terms, when available, and keywords: Ovid MEDLINE ALL (1946–January 5, 2022), Embase (through Elsevier, 1947–present), Web of Science Core Collection (through Thomson Reuters, including Science Citation Index Expanded, 1974–present, and Social Sciences Citation Index, 1974–present), ScienceDirect (Elsevier) Journals & Books, and CAB Direct (including CAB Abstracts and Global Health; last updated on January 4, 2022). Searches were developed in Ovid MEDLINE and translated to additional databases. Results were limited to publication dates from 2008 to present and English language, and systematic reviews and reviews were excluded when possible. Duplicates were removed with the use of Covidence systematic review software, which was also used for screening and full-text review. See Appendix 1 (http://links.lww.com/AOG/D543) for a complete list of all database search strategies. The search was rerun in April 2023 to identify any new publications, and the concept of serous was removed from the search strategy. The systematic review has not been registered in PROSPERO. All included articles were included in the updated search, so only the updated search strategy is accounted for in the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) diagram and appendices.

Citations and abstracts were uploaded in Covidence for study selection. As a measure of certainty or confidence, all the selected articles were confirmed to be peer reviewed. Two authors (B.G.B., E.R.W.) independently screened all titles and abstracts. Articles considered for inclusion were independently reviewed by two authors, and consensus was reached by discussion on any conflicting articles selected for inclusion. Although both reviewers are ovarian cancer specialists, there is noted potential for selection bias of the reviewers resulting from an emphasis in their basic science training. Literature was compiled in Covidence; the PRISMA figure was generated with Covidence, and the tables were developed with Excel.

Sensitivity is the ability of a positive test to correctly identify an individual with the disease being tested. Specificity is the ability of a negative test to correctly identify an individual who does not have the disease being tested. The AUC is taken from a receiver operating characteristic curve. It is a way to quantify the ability of a test to determine a whether a person has a disease or does not have a disease. An AUC of 1.0 would be able to distinguish disease from nondisease perfectly, whereas an AUC of 0.5 would be no better than chance in determining disease compared with nondisease.[16]

RESULTS

In the five major repositories, 5,523 related articles were uploaded to Covidence. After the removal of duplicates, 3,747 related articles matched our search terms (Appendix 2, available online at http://links.lww.com/AOG/D543). Further screening by two independent reviewers of the article abstracts led to the identification of 245 peer-reviewed primary research articles for full-text review. After full-text review by two independent reviewers, removal of duplicate articles led to the identification of 131 peer-reviewed primary research articles (Fig. 1 PRISMA flow diagram, Table 1, and Appendix 3, available online at http://links.lww.com/AOG/D543). Seven clinical trials were identified by the ClinicalTrials.gov query, and three were directly related to early diagnosis (NCT04794322, NCT05146505, and NCT03622385); however none had reported outcomes. Given the expertise of the reviewers, the systematic approach for article selection, and the a priori criteria, the 131 articles identified in the five literature repositories are deemed to be high-confidence selections. Thus, these 131 articles serve as the source of the remainder of this systematic literature review.

As of 2007, early-stage high grade serous carcinoma was appreciated to occur predominantly in the fallopian tube. Consistently, a review of the 131 articles revealed that more than 88.5% of the articles that examined or used fallopian tube epithelium as a comparator to identify novel strategies for high-grade serous carcinoma early detection were published after 2015 (Appendix 4, available online at http://links.lww.com/AOG/D543). The 131 articles were published in 78 different peer-reviewed journals, with *Gynecologic Oncology* representing the majority at 7.6% (10/131).

The design and results of the 131 selected articles were further examined. A summary of the study selection and characteristics can be found in Table 1. Nearly 91.6% of the articles (120/131) were retrospective and examined specimens already collected; 6.8% (9/131) were prospective studies (studying characteristics that predate diagnosis) to evaluate an early-stage biomarker. Two studies (1.5%) conducted both

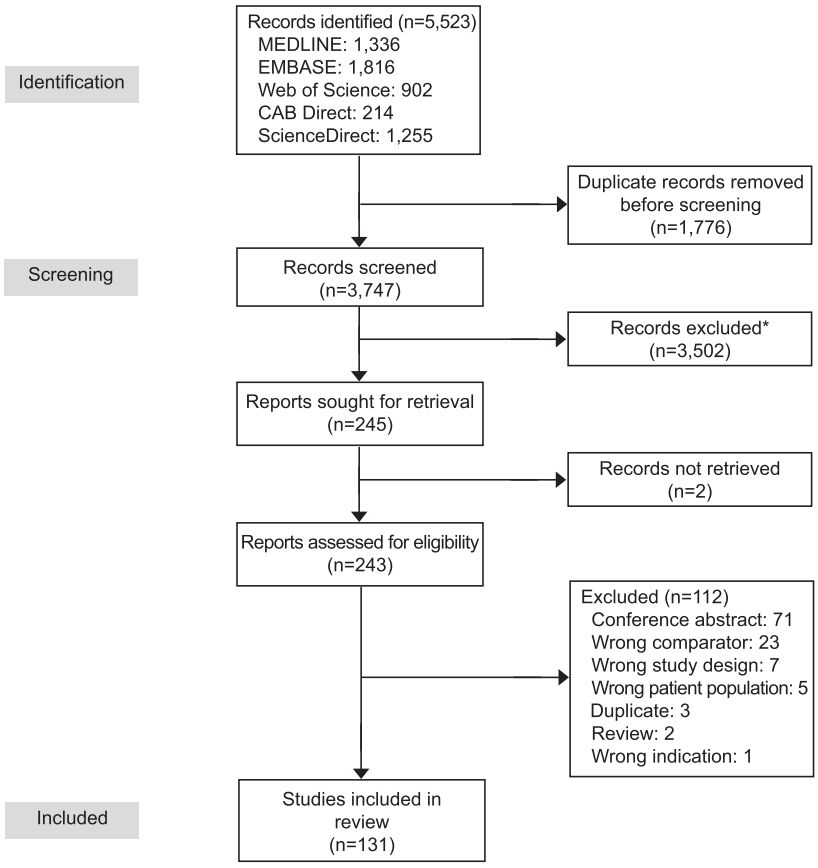

Fig. 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram for new systematic reviews that included searches of databases and registers only. *All records excluded were because of selection by two independent reviewers. Any conflicts were discussed, and the final decision was made by one reviewer (B.B.).

Greenwood. Ovarian Cancer Early Detection Coming of Age. Obstet Gynecol 2024.

retrospective and prospective studies. The sample size across the 131 studies ranged from 6[17] to 66,450.[18] Most studies reported only a discovery cohort, whereas 34 studies validated their findings through either independent data sets (20 studies) or cross-validation methods (14 studies). Of the 131 studies, 55 reported sensitivity, specificity, or AUC, with 30 of the studies reporting at least one biomarker with an AUC greater than 0.9. These findings suggest that appropriate methods for biomarker identification and classification remain underutilized.

More than 45.8% of the studies (60/131) examined a protein, peptide, or posttranslational protein modification as a biomarker for early detection, and some studies aimed specifically to identify new markers that, when used in combination, would improve the diagnostic performance of CA 125 or other conventional tests. Twenty-four studies measured only a single protein, and none of these studies reported a sensitivity of greater than 80%. Urunsak et al[19] examined serum adenosine deaminase and were able to differentiate between ovarian cancer and benign tumors at 84% sensitivity and 80% specificity (AUC 0.82); however, peritoneal fluid adenosine deaminase did not perform as well. Another study examined plasma-derived annexin A2 and reported a sensitivity of 80% at 99.6% specificity for distinguishing patients with high-grade serous carcinoma stage IA from healthy individuals in a control group when combined with CA 125 (AUC 0.970 when combined with CA 125, AUC 0.774=annexin A2 alone).

Thirty identified studies examined multiple proteins alone or with other biomarkers, including metabolites and microRNAs. Combination of multiple biomarkers tended to improve sensitivity or AUC; 12 of 30 studies reported greater than 80% sensitivity or an AUC greater than 0.9 (Table 2). Huh et al[20] assessed an 18-protein model that showed sensitivity of 100% and specificity of 91% in distinguishing patients with high-grade serous carcinoma from healthy patients (AUC 0.99). Kampan et al[12] assessed serum levels of interleukin-6 and human epididymis protein 4 in patients with high-grade serous carcinoma ovarian cancer, a benign mass, or normal ovaries and reported sensitivity and specificity at 100% with an AUC of 1.0. Five studies examined posttranslational protein modification in which only one reported an AUC[21]

Table 1. Summary of Study Selection and Characteristics

Characteristic	Value
Study design (n=131)	
Retrospective	120
Prospective	9
Both	2
Comparison	
Healthy vs cancer	37
Precancer vs cancer	12
FTE vs cancer	9
OSE vs cancer	7
Multicomparisons	43
BRCA wild type vs *BRCA1* mutated	1
Healthy vs precancer	2
Mixed comparisons	20
No. of specimens	
Normal or precancer	98,496 (3, 40,941)
Cancer	64,038 (3, 25,509)
Factor examined or biological source	
Tissue	43
Blood	46
Urine	2
Proximal fluid	5
Medical record	1
Imaging	0
Publicly available data (eg, TCGA)	1
Cell line	1
Metadata analysis	1
Mixed	31
Readout	
Clinical attribute	2
Protein	42
RNA	23
DNA	11
Metabolite	4
Posttranslational modification	1
Chromatin	0
Cytology	1
DNA methylation	4
Fluorescence	1
Iron or zinc	1
Vibrational spectral absorbance	3
Mixed (2 readouts)	32
Mixed (3–4 readouts)	6

FTE, fallopian tube epithelium; OSE, ovarian surface epithelium; TCGA, The Cancer Genome Atlas.
Data are n or total N (minimum, maximum).

that reached a level greater than 0.9 when a panel of antiproteoglycans (5 glycans) were combined with CA 125 testing.

Epigenetic changes are defined by a modification or regulation of genetic programming without changes to the underlying genetic sequence. Numerous studies have demonstrated aberrant epigenetic regulation in the process of cellular transformation to cancer. In our literature review, 27 studies incorporated an epigenetic biomarker to aid in the detection of early-stage high-grade serous carcinoma. Eleven studies examined DNA methylation; one study examined transfer RNA; and one study examined PAX8 (müllerian marker) DNA binding. Pisanic et al[22] reported high-grade serous carcinoma–specific differentially hypermethylated regions with an AUC greater than 0.9; specifically, hypermethylation on the *PCDHB12* gene reported an AUC of 0.958 when serous tubal intraepithelial carcinoma was compared with paired adjacent-normal fallopian tube epithelium, and the *C17orf64* gene reported an AUC 0.924 high-grade serous carcinoma compared with healthy fallopian tube epithelium. Pisanic et al[23] observed hypermethylation of loci within two genes that demonstrated an AUC greater than 0.9, *c17orf64* (AUC 0.968) and *IRX2* (AUC 0.928), for detecting high-grade serous carcinoma compared with samples from healthy individuals. Moreover, the combination of *c17orf64+IRX2+TUBB6* (three top-performing markers) resulted in an AUC of 1.0 for detecting high-grade serous carcinoma compared with samples from healthy individuals.

MicroRNA accounted for 14 of these studies, six of which examined members of the microRNA 200 family (eg, microRNA 200c). Four studies reported a sensitivity of 80% or greater or an AUC of 0.9 or greater for detecting cancer compared with noncancer,[24,25] and only one reported an AUC of 0.9 or greater.[24] An ongoing clinical trial, NCT05146505, is leveraging microRNA as an early diagnostic tool.

During the progression of fallopian tube epithelium to high-grade serous carcinoma, appreciable genetic mutations are predicted to occur in nearly all high-grade serous carcinoma cells. For instance, mutation of TP53 (p53) tumor suppressor is nearly ubiquitous in high-grade serous carcinoma tumors, with 75–98% of high-grade serous carcinoma tumors harboring a p53 mutation.[26] In addition, nearly 50% of high-grade serous carcinoma tumors harbor mutations in genes involved in DNA double-strand break repair (eg, *BRCA1*, *BRCA2*, *PALB2*).[26,27] The consequence of impaired DNA double-strand break repair is high frequency of chromosomal instability (eg, amplifications, translocations). In the literature we reviewed, 14 studies examined gene mutations, with six studies reporting a sensitivity of 80% or greater or an AUC of 0.9 or greater. In the work by Erickson et al,[28] p53 mutations were determined in blood isolated from tampons of patients with or without high-grade serous carcinoma, and although all eight high-grade serous carcinoma tumors harbored a p53 mutation in the

Table 2. Published Studies With Reported Specificity (80% or Greater) or Area Under the Curve (0.9 or Greater)

Primary Readout Focus	Biospecimen	Effect on marker(s)	AUC (95% CI)	Sensitivity (%) (95% CI)	PMID
Protein, peptides, or posttranslational modification	Tissue	Tissue TOP1, PDIA4, and OGN expression profiles highly discriminatory		98.2	35197484
Protein, peptides, or posttranslational modification	Blood	Panel of CA 125, HE4, E-CAD, and IL-6 distinguished early-stage HGSC from nonmalignant control samples with higher efficacy than CA 125, HE4, or CA 125+HE4	0.961±0.0243	84.2	29572027
Protein, peptides, or posttranslational modification	Blood	84 upregulated, 32 downregulated proteins in serum from patients with HGSC vs healthy individuals in a control group	0.99	100.0	35939567
Protein, peptides, or posttranslational modification	Blood	Serum IL-6 distinguishes among HGSC, benign ovarian masses, and control samples without malignancy; diagnostic value highest when IL-6 is combined with CA 125 and HE4.	IL-6: 0.962 (0.926–0.998) IL-6+CA 125: 0.985 (0.966–1.000) IL-6+HE4: 1.000 (1.000–1.000)		32042020
Protein, peptides, or posttranslational modification	Blood	Combination of TNRF2+Tregs and IL-6 in blood of advanced-stage HGSC discriminates benign ovarian masses from control samples without malignancy.	1.000 (1.000–1.000)		36765633
Protein, peptides, or posttranslational modification	Blood	Machine learning was able to predict EOC diagnosis and EOC stage based on several blood-borne CRP, lymphocyte count, and CA 125	Conditional random forest: 0.978 Gradient-based machine: 0.976 Random forest: 0.968		30,979,733
Protein, peptides, or posttranslational modification	Blood	Plasma ANXA2 elevated in early-stage (I and II) HGSC vs control samples without malignancy; ANXA2 with CA 125 test highly diagnostic of early stage OC	0.969	84.4	33406648

(*continued*)

Table 2. Published Studies With Reported Specificity (80% or Greater) or Area Under the Curve (0.9 or Greater) (*continued*)

Primary Readout Focus	Biospecimen	Effect on marker(s)	AUC (95% CI)	Sensitivity (%) (95% CI)	PMID
Protein, peptides, or posttranslational modification	Blood	Serum protein Z, fibronectin, CRP, and CA 125 effective in predicting OC occurrence 2–3 y before diagnosis	0.944 (0.896–0.992)		27903971
Protein, peptides, or posttranslational modification	Blood	Incorporating longitudinal measurement of serum CA 125, HE4, CHI3L1, PEBP4, or AGR2 predicted OC (particularly HGSC) up to 1 y before diagnosis.	CA 125+PEBP4: 0.97 (0.934–1.000) CA 125+CHI3L1: 0.986 (0.973–0.999) CA 125+AGR2+CHI3L1: 0.984 (0.971–0.998) CA 125+HE4: 0.988 (0.976–1.000)	CA 125+PEBP4: 95.5 (77.3–100.0) CA 125+CHI3L1: 100.0 (90.9–100.0) CA 125+AGR2+CHI3L1: 100.0 (90.9–100.0) CA 125 + HE4: 100.0 (86.4–100.0)	31937926
Protein, peptides, or posttranslational modification	Blood	Plasma antibodies against HSF1 and CCDC155 are elevated in early-stage HGSC and are superior to CA 125; combined measurement improved sensitivity and efficacy of detection	HSF1: 0.95 CCDC155: 0.80		29,141,850
Protein, peptides, or posttranslational modification	Blood	Increased serum MMP-9, Hpa, and CL levels in patients with OC vs healthy individuals in a control group and patients with benign ovarian mass; patients with low-grade and advanced-stage vs high-grade and early-stage disease	0.935	96.4	23359763
Protein, peptides, or posttranslational modification	Proximal fluid	Increased GJA1, C4BPB, ATP2B4, VPS11, and TMEM67 expression and decreased KIF20B expression in HGSC proximal fluid vs nonmalignant control proximal fluid	C4BPB+KIF20B: 0.979 (0.953–1.00) VPS11+CRTAC1 +TMEM67: 0.968 (0.938–0.999) GJA1+ATP2B4: 0.943 (0.889–0.997)		36214786
Protein, peptides, or posttranslational modification	Blood, proximal fluid	Elevated serum and ovarian cyst fluid ALDOA diagnostic in early-stage EOC (low grade and high grade) with (LC)-MS/MS.	0.96		30710757

(*continued*)

Table 2. Published Studies With Reported Specificity (80% or Greater) or Area Under the Curve (0.9 or Greater) (*continued*)

Primary Readout Focus	Biospecimen	Effect on marker(s)	AUC (95% CI)	Sensitivity (%) (95% CI)	PMID
Protein, peptides, or posttranslational modification	Blood, proximal fluid	Serum and proximal fluid ADA upregulated in patients with HGSC vs patients with benign ovarian mass	Serum ADA: 0.82 Peritoneal fluid ADA: 0.78	Serum ADA: 84.0 Peritoneal fluid ADA: 74.0	22395862
Protein, peptides, or posttranslational modification/ DNA mutational profiles	Blood	Increased circulating histone-DNA complex, cfDNA, neutrophil elastase, prekallikrein, and CA 125 in patients with HGSC vs healthy individuals in a control group	0.966 (0.933–1.000)	97.3	36620601
Protein, peptides, or posttranslational modification/ DNA mutational profiles	Blood, proximal fluid	Increased NETosis biomarkers (cfDNA, nucleosomes, citrullinated histone 3, calprotectin, and myeloperoxidase) in serum and peritoneal fluid from patients with HGSC vs healthy individuals in a control group	cfDNA: 0.90 (0.80–1.00) Nucleosomes: 0.94 (0.87–1.00) CitH3: 0.96 (0.92–1.00) Calprotectin: 0.91 (0.84–1.00) Myeloperoxidase: 0.87 (0.77–0.98)		36817483
Epigenetics	Tissue	Whole-methylome sequencing identified novel OC methylated-DNA markers; differentiated 63/73 cases with HGSC included 5/5 with stage I or II disease	0.91 (0.86–0.96)	79 (69–87)	35370009
Epigenetics	Tissue	Elevated methylation in promoter regions of TUBB6, IRX2, and c17orf64 in HGSC and precursor STICs vs control samples without malignancy	1.0	100.0	30108103
Epigenetics	Tissue	Methylation landscape of STICs intermediate between normal FTE and HGSC tumors	*PCDHB12*: 0.958		32817081
Epigenetics	Blood	Serum miR200a, b, and c higher in patients with serous EOC vs a control group of individuals without malignancy; combined miR200b+c best predictive qualifier	miR-200a: 0.675 miR-200b: 0.722 miR-200b+c: 0.784	miR-200a: 85.7 miR-200b: 85.7 miR-200b+c: 78.6	23272653

(*continued*)

Table 2. Published Studies With Reported Specificity (80% or Greater) or Area Under the Curve (0.9 or Greater) (*continued*)

Primary Readout Focus	Biospecimen	Effect on marker(s)	AUC (95% CI)	Sensitivity (%) (95% CI)	PMID
Epigenetics	Blood	Upregulated serum exosomal miR-93, miR-145, and miR-200c in HGSC samples vs non-HGSC cases, benign, and borderline groups; specificity and sensitivity superior to CA 125	miR-145: 0.910 (0.840–0.980) miR-200c: 0.802 (0.698–0.906)	miR-145: 91.7 miR-200c: 72.9	31205555
Epigenetics	Blood	Model with 18 differentially methylated DNA regions (cfDNA) able to differentiate patients with OC from patients without malignancy	0.967 (0.940–0.994)	94.7 (85.4–98.9)	35973389
Epigenetics	Blood	miR-1246 overexpressed in both serum and tumors of patients with HGSC vs individuals in a control group without malignancy	0.893	87	28017893
Epigenetics	Blood, cell line	Serum miR1290a elevated in patients with HGSC vs patients with other histotypes and individuals in a control group without malignancy; serum levels more effective at detection than CA 125 alone and positively associated with FIGO stage	miR-1290: 0.71 CA 125+miR-1290: 0.97	miR-1290: 63	30,219,071
Epigenetics/RNA	Tissue	Lower CDH13, HNF1B, PCDH17, and GATA4 gene expression in HGSC tumors vs nonmalignant control tissue, particularly in those samples with high gene methylation		88.5	32145055

(*continued*)

Table 2. Published Studies With Reported Specificity (80% or Greater) or Area Under the Curve (0.9 or Greater) (*continued*)

Primary Readout Focus	Biospecimen	Effect on marker(s)	AUC (95% CI)	Sensitivity (%) (95% CI)	PMID
Epigenetics/RNA	Blood	RASSF1A promoter methylation increased in patients with EOC vs healthy individuals in a control group; HGSC vs LGHOC, advanced stage vs early stage	Serum RASSF1A: 0.993 (0.96–0.99)	Serum RASSF1A: 97 *RASSF1A* promoter methylation: 85	29098560
DNA mutational profiles	Tissue	Using 49 different copy number variant loci, can differentiate EOC from FT, AUC 1.0	1.00 (1.00–1.00)		36499142
DNA mutational profiles	Blood	Comparing HGSC blood copy number index score with that of healthy individuals in a control group detects cancer		91.0	35008332
DNA mutational profiles	Blood	Higher plasma cfDNA in patients with OC vs a control group of individuals without malignancy, positively associated with copy number alterations and FIGO stage	0.94	78.0	27852697
DNA mutational profiles	Blood	Alterations in circulating cfDNA can be combined with CA 125 to improve differential diagnosis of OC.	0.9752	96.0	34053311
Metabolite	Blood	Alterations in several mouse serum metabolites detectable, differentiating between non-HGSC samples (control mice) and early and advanced HGSC (triple KO mice)		96.2	31290664
Metabolite	Blood	Serum levels of 147 lipid species between patients with HGSC and healthy individuals in a control group; 100 species different between stage I–II and control samples; lipid levels also varied by disease stage (I–II vs III–IV)	1.0	100.0	35495636

(*continued*)

Table 2. Published Studies With Reported Specificity (80% or Greater) or Area Under the Curve (0.9 or Greater) (*continued*)

Primary Readout Focus	Biospecimen	Effect on marker(s)	AUC (95% CI)	Sensitivity (%) (95% CI)	PMID
Metabolite	Urine	Increased urine N^1,N^{12}-diacetylspermine levels in OC vs tumor-free individuals in a control group, HGSC vs low malignant; potential patients, patients with stage III–IV vs stage I–II, stage I–II vs benign tumor	0.83	86.5	28604456
Metabolite	Blood, tissue	Increased plasma C16-Cer, C18:1-Cer, C18-Cer in HGSC ([+]: FIGO stage); increased tissue C16-Cer, C18:1-Cer, C18:Cer, C24:1-Cer, C24-Cer and SIP and decreased SPH in HGSC vs normal tissue	C18:1-Cer: 0.768 (0.53–0.81) C18-Cer: 0.771 (0.53–0.8) C16-Cer: 0.759 (0.51–0.8)	C18:1-Cer: 90.0 (59.6–98.5) C18-Cer: 80.0 (50.0–94.7) C16-Cer: 77.0 (56.5–94.3)	28800942
Metabolite/RNA	Blood, tissue	Increased circulating lactate in patients with HGSC, increased HCAR1 mRNA and protein expression in OC tissue vs healthy control sample	0.969 (0.940–0.998)		36615018
Metabolite/RNA	Blood, tissue, public dataset	Increased hydroxybutyric acid metabolites in sera and tumors from patients with HGSC vs a control group of individuals without malignancy	0.91		26685161

AUC, area under the curve; HGSC, high-grade serous carcinoma; HE4, human epididymis protein 4; IL-6, interleukin 6; Treg, regulatory T cell; EOC, epithelial ovarian cancer; CRP, C-reactive protein; ANXA2, annexin A2; OC, ovarian cancer; MMP, matrix metalloproteinase; EOC, epithelial ovarian cancer; ADA, adenosine deaminase; STIC, serous tubal intraepithelial carcinoma; FTE, fallopian tube epithelium; miR, microRNA; FIGO, International Federation of Gynecology and Obstetrics; FT, fallopian tube.

tumor, only three of the eight blood samples from tampons showed the mutation. In the Gonzalez-Bosquet et al report,[29] a model of 49 single nucleotide variants had excellent performance with an AUC of 1.0 in distinguishing high-grade serous carcinoma from benign fallopian tube; models with 11 copy number variants (AUC 0.87) and 17 structural variants (AUC 0.73) performed more poorly. In the study by Vanderstichele et al,[30] chromosomal copy number from cell-free DNA was examined in a total of 112 patients (44 healthy control group, 57 high-grade serous carcinomas or borderline, 11 benign), and they reported a specificity of 99.6% and sensitivity of 78% when benign tumors were compared with high-grade serous carcinoma tumors. As sequencing technologies continue to become more cost effective with increased sensitivity, the ability to scale up sequencing-based biomarkers becomes more attainable.

In addition to DNA, RNA and RNA profiles have been proposed to be viable biomarker for cancer progression. Thirteen studies evaluated multiple gene expression, and two studies examined circular RNA expression; however, only two studies reported sensitivity and specificity and AUC, and neither of these reported a sensitivity of 80% or greater or an AUC of 0.9 or greater. Notably, Dinh et al[31] performed single-cell RNA sequencing on 12 normal fallopian tubes and identified 10 distinct subpopulations for epithelial cells. The investigators further used the underlying transcriptomic profiles to develop a differentiation trajectory between the different cell types. Next, using the transcript profiles for each population, the investigators were able to deconvolute RNA-sequencing data from high-grade serous carcinoma tumors and to identify the precursor epithelial subpopulation responsible for the high-grade serous carcinoma tumor. This highlights the use of both sequencing and advanced computational analysis to further elucidate the transformation of fallopian tube epithelium to advanced high-grade serous carcinoma. Furthermore, this study highlights the power of sequencing nucleic acids from the serum or tumor compartment for diagnostic purposes and thus remains a major area of research.

Cancer-associated metabolic reprogramming offers a unique opportunity to track disease progression and serve as a biomarker for early-stage disease. It is notable that reports have shown an increased dependence on lipid metabolism during high-grade serous carcinoma progression.[32–34] In the literature reviewed here, seven studies evaluated metabolites in serum, tissue, or ascites. All but one reported sensitivity or AUC; all reported a sensitivity of 80% or greater or an AUC of 0.9 or greater. For instance, Niemi et al[35] performed lipidomic analysis on the sera of 354 patients (malignant n=138, borderline n=25, healthy control group n=191). The investigators observed 39 lipid species elevated in both early- and late-stage disease. Lipid species increased with increasing stage. Ceramide (d18:1/18:0), a type of sphingolipid, was notably elevated in both high-grade serous carcinoma tumors and premenopausal compared with postmenopausal individuals. The rise in lipids seemed to be restricted to the high-grade serous carcinoma histotype. Furthermore, in stage I–II disease, combining lipid profiles with CA 125 reported an AUC of 0.87 compared with CA 125 alone, which reported an AUC of 0.69. As discussed later, the ability to serial test through a noninvasive blood draw is an attractive approach for the development of an early high-grade serous carcinoma diagnostic tool.

DISCUSSION

The ability to detect early-stage ovarian cancer has represented a significant area of research for the past 4 decades. Parallel to researching suitable biomarkers, the understanding of ovarian cancer cause, tumorigenesis, and progression has significantly advanced, especially in the past 15 years. Because the fallopian tube is appreciated to be the primary site of high-grade serous carcinoma tumorigenesis, there has been a shift in the early-stage biomarker research to include normal fallopian tube or adjacent normal fallopian tube as a comparator against high-grade serous carcinoma tumors. In this systematic review, there was an attempt to summarize the primary research literature published since 2008 that focused primarily on early detection of fallopian tube–derived ovarian cancers.

Through the literature review, a multitude of biomarkers and strategies were highlighted that have been investigated, including nucleic acid, protein, and metabolic biomarkers. Although most reported biomarkers alone failed to improve detection compared with CA 125, several studies combined the novel biomarker alone and in combinations with CA 125 or human epididymis protein 4 (eg, annexin A2, adenosine deaminase). In most of these cases, the combined test showed an ability to distinguish between fallopian tube epithelium and malignancy that trends toward marginal improvement over single-marker testing.

As noted through our literature search, 27.4% of the studies (36/131) have demonstrated diagnostic tests with 80% or greater specificity or an AUC of 0.9 or greater. As a reference for future work, Table 2 list these studies with the readout and specific findings for each report. These studies should be used to guide future biomarker development.

As the research effort to detect high-grade serous carcinoma as a precursor lesion or as an early-stage disease continues, we would like to highlight, in the context of this systematic review, areas of potential future research that may aid in the development of a clinically meaningful diagnostic test. These areas include expanded use of proximal fluid, serial sampling, upscaling of a diagnostic test, and improvement in clinical uptake.

Frequently, high-grade serous carcinoma progression and dissemination are independent of hematogenous involvement, which highlights the limited utility of identifying circulating tumor cells or macromolecules as an “early” biomarker. It is notable that improved technological sensitivity of detection for blood-based biomarkers will likely overcome this

limitation, but a more immediate solution may be the use of proximal fluids, such as uterine lavage. Several studies have used uterine lavage in patients at high risk (ie, *BRCA* carriers) paired with proteomics or genomics techniques to detect ovarian cancer with mixed results in detecting early-stage disease.[36–38] Examination of biomarkers from uterine lavage may represent an approach to overcome a key limitation noted by UKCTOCS that stage shifting from III–IV to I–II was not sufficient to improve overall survival.[5] An active, recruiting clinical trial (NCT04794322) is assessing DNA derived from uterine lavage.

The use of CA 125 and human epididymis protein 4 is sufficient to detect large-burden, advanced-stage disease, which is evidenced by the fact that after surgical interventions these biomarkers often fall to within normal limits despite the subsequent high disease recurrence rates.[39,40] A strategy to address the limited sensitivity is to use serial sampling of CA 125 or human epididymis protein 4 compared with a single threshold to inform clinical decisions.[41] By extension, the implementation of a novel biomarker should incorporate serial sampling to improve both high-grade serous carcinoma detection and longitudinal understanding of high-grade serous carcinoma progression. The serial sampling may allow better understanding of patient baselines and normal physiologic fluctuations. However, the economic effects of serial sampling must be considered; biomarker testing can add to patient and health system financial toxicity. Another consideration is the likely anxiety and potential downstream effects of small changes in biomarkers, leading to ultimately unnecessary procedures for nonmalignant processes.

A noted limitation is that although demographic information, including race, is included, the data frequently are skewed toward a predominately White cohort and may miss crucial data from minority populations. It is established that there are differences in CA 125 levels among Black and Latinx individuals, who show lower baseline CA 125 levels than their White counterparts, making it more likely that a diagnosis might be missed or delayed if based solely on CA 125 levels.[42] In addition, there was an emphasis on early detection of the high-grade serous carcinoma subtype using the fallopian tube as the "normal" or healthy comparator; thus, there is limited extension of the reported findings to other ovarian cancer histologic subtypes. Most of the studies are retrospective in nature, which makes it challenging to understand both experimental and selection bias.

Converting novel, research-based diagnostic tests to clinically used tests represents a significant hurdle because of several factors, including but not limited to manufacturing, development costs, improvement of existing tests, overall low incidence of the disease, health care professional hesitancy, technical training, and data interpretation. Therefore, these factors need to be addressed with research at a similar level of investment as novel biomarker development itself.

Finally, there would likely be hesitancy from health care professionals to adopt new biomarker testing without evidence of significant improvements in detection rates compared with current standards. Decisions about the clinical implications and a consensus on the interventions to be recommended if there were abnormalities in the new biomarkers need to be established. For example, there currently is limited evidence for and consensus on the management of serous tubal intraepithelial carcinoma lesions when detected.[43] In parallel with evaluation of new potential biomarkers, it will be critical to generate prospective data that support the management of early-stage disease and detection of precancerous lesions, leading to clinically meaningful improvements in outcomes.

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