Systematic Review

Circulating Tumor DNA for Early Prediction of Relapse in Epithelial Ovarian Cancer: A Systematic Review and Meta-analysis

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Abstract

Background: Relapse remains the principal cause of mortality in epithelial ovarian carcinoma, and current surveillance approaches relying on radiologic imaging and protein biomarkers such as cancer antigen 125 (CA 125) frequently detect recurrence only after macroscopic disease has developed. Circulating tumour DNA (ctDNA) has emerged as a promising biomarker of minimal residual disease (MRD), potentially enabling earlier detection of molecular relapse. **Material and Methods:** We conducted a systematic review and meta-analysis in accordance with PRISMA 2020 guidelines to evaluate the prognostic performance of post treatment ctDNA detection for early relapse prediction in epithelial ovarian cancer. PubMed was searched from January 2010 to October 2025 for prospective and retrospective studies assessing plasma ctDNA after definitive therapy. Eligible studies reported relapse related outcomes and included comparative data with established biomarkers where available. Hazard ratios (HRs) for recurrence were pooled using a random effects model. Diagnostic accuracy was assessed using a hierarchical summary receiver operating characteristic (HSROC) model. **Results:** Four studies comprising 410 patients met inclusion criteria for quantitative synthesis. Post treatment ctDNA positivity was consistently associated with significantly shorter progression free survival. Pooled analysis demonstrated an approximately three fold increased risk of recurrence among ctDNA positive patients (HR = 2.83; 95% CI 1.82–4.40), with moderate heterogeneity ($I^2 = 68\%$). Tumour informed assays exhibited substantially stronger prognostic discrimination than tumour naïve panels. Diagnostic meta-analysis showed a pooled sensitivity of 0.71 (95% CI 0.60–0.82) and specificity of 0.92 (95% CI 0.84–0.96), with an area under the curve of 0.91. Across comparative cohorts, ctDNA detected molecular relapse a mean of 6.9 months earlier than radiologic progression and consistently outperformed CA 125 in both lead time and specificity. **Conclusion:** Post treatment ctDNA is a highly specific and clinically meaningful biomarker of minimal residual disease in epithelial ovarian carcinoma, providing earlier and more accurate relapse detection than conventional protein biomarkers. These findings support the integration of ctDNA into postoperative surveillance strategies and highlight the need for prospective interventional trials to determine whether ctDNA guided management improves survival outcomes.

Keywords: Circulating tumor DNA, Ovarian cancer, Minimal residual disease, Relapse, CA-125, Biomarkers, Recurrence.

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Introduction

Despite advances in surgical cytoreduction and systemic therapy, relapse remains the principal cause of mortality in epithelial ovarian carcinoma and many other solid tumors. Current post-treatment surveillance strategies rely predominantly on radiologic imaging and serum protein biomarkers, such as cancer antigen-125 (CA-125) or carcinoembryonic antigen (CEA), which often detect recurrence only after macroscopic disease has developed. There is therefore a critical need for biomarkers capable of identifying molecular relapse earlier, enabling improved risk stratification and potentially more timely therapeutic intervention.

Circulating tumor DNA (ctDNA), the fraction of cell-free DNA derived from tumor cells, has emerged as a promising biomarker of minimal residual disease (MRD). Across multiple tumor types—including breast, colorectal, lung, ovarian, melanoma, and others—ctDNA detection after definitive therapy (post-operative or post-adjuvant) or during longitudinal surveillance has been consistently associated with a substantially increased risk of relapse and inferior disease-free and overall survival. Multiple systematic reviews and meta-analyses have demonstrated that ctDNA positivity following curative-intent treatment confers a several-fold higher hazard of recurrence, underscoring its value as a prognostic indicator of occult residual disease.[1-3]

A key strength of ctDNA-based MRD assays is their high specificity for subsequent clinical recurrence, with false-positive results being uncommon. However, sensitivity is variable and influenced by tumor biology, disease burden, assay design, and timing of sampling. Evidence suggests that sensitivity improves with serial surveillance testing rather than single landmark

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sampling, and with the use of tumor-informed, personalized assays that track patient-specific somatic mutations rather than tumor-agnostic panels.[4-6] These methodological considerations are particularly relevant in ovarian cancer, where peritoneal-predominant disease and variable tumor shedding may limit detection at a single time point.

Head-to-head comparisons where available indicate that ctDNA outperforms traditional protein biomarkers, including CA-125, CEA, and CA19-9, in both the timing and accuracy of relapse detection. In ovarian cancer specifically, several prospective cohorts have demonstrated that postoperative ctDNA detection precedes CA-125 elevation and radiologic recurrence by several months, and more accurately identifies patients at high risk of early relapse.[7-9] These findings suggest that ctDNA may overcome important limitations of existing biomarkers, particularly in histologic subtypes or clinical scenarios where CA-125 is uninformative.

More recently, ctDNA has moved beyond retrospective and observational studies into prospective and interventional research. A ctDNA-guided randomized trial and multiple large prospective cohorts have provided stronger evidence that ctDNA status can stratify recurrence risk and inform decisions regarding treatment escalation or intensified surveillance.[10,11] However, results remain heterogeneous, and definitive evidence that ctDNA-guided intervention improves survival outcomes is still lacking. Consequently, while ctDNA is increasingly recognized as a powerful prognostic and surveillance biomarker, its optimal clinical integration—particularly in ovarian cancer—remains an area of active investigation.

In this context, we conducted a systematic review and meta-analysis to evaluate the efficacy of post-surgery ctDNA-based MRD detection for early prediction of relapse in epithelial ovarian cancer, with specific comparison to established biochemical biomarkers such as CA-125 and CEA. By focusing on post-treatment MRD endpoints and excluding small or non-comparative studies, this analysis aims to provide a rigorous and clinically relevant synthesis of the current evidence base.

Materials and Methods

This systematic review and meta-analysis were conducted in accordance with the PRISMA 2020 reporting guidelines.[9] Eligible studies included women with epithelial ovarian cancer who underwent definitive therapy and had plasma ctDNA assessed postoperatively or during surveillance for MRD. Outcomes of interest included recurrence, progression-free survival (PFS), disease-free survival (DFS), and lead time to radiologic relapse.

A systematic search of PubMedwas performed from January 2010 to October 2025 the search strategy was:

("ovarian cancer" OR "epithelial ovarian") AND
("circulating tumor DNA" OR ctDNA OR "cell-free DNA") AND
("minimal residual disease" OR MRD OR postoperative OR post-surgery OR posttreatment) AND
(relapse OR recurrence OR progression)
NOT (review OR protocol)

Searches were restricted to human studies published in English. Reference lists of eligible studies and relevant reviews were manually screened to identify additional publications. ClinicalTrials.gov was searched to identify ongoing or unpublished studies for contextual interpretation. References lists of eligible studies were manually screened.

Risk of bias was assessed independently by two reviewers using the Quality in Prognosis Studies (QUIPS) tool, which evaluates bias across six domains relevant to prognostic biomarker studies.[10] Disagreements were resolved by consensus.

For quantitative synthesis, hazard ratios (HRs) comparing ctDNA-positive and ctDNA-negative patients were extracted directly or estimated from Kaplan–Meier curves where required. Pooled estimates were calculated using a random-effects model with restricted maximum likelihood (REML). Statistical heterogeneity was assessed using the I^2 statistic and τ^2.[11] Diagnostic accuracy was evaluated using a hierarchical summary receiver operating characteristic (HSROC) model based on bivariate random-effects regression.[1]

Results

A comprehensive search of PubMed, Embase, Scopus, and supplementary sources identified 321 publications relevant to circulating tumor DNA (ctDNA) in ovarian cancer. After removal of 83 duplicates, 238 titles and abstracts were screened, and 24 full-text articles were assessed for eligibility. Twenty studies were excluded: eight due to small sample size (<50 participants), six that evaluated ctDNA in recurrent or metastatic-only settings, four that focused solely on assay validation without clinical outcomes, and two that were non-English. Four studies met all inclusion criteria and were included in the quantitative synthesis [Figure 1], (PRISMA flow). Two additional small but relevant studies (Chao et al., 2023; Kfoury et al., 2023) were retained in the qualitative review but excluded from meta-analysis owing to sample size limitations (<50 patients).

The four included studies—Hou et al. (2022), Zhang et al. (2024), Kallio et al. (2024), and Heo et al. (2024)—comprised a total of 410 evaluable patients with epithelial ovarian carcinoma who had undergone primary cytoreductive surgery and adjuvant chemotherapy. All assessed ctDNA in plasma samples obtained after definitive treatment, with relapse or disease progression as primary outcomes. Tumor-informed next-generation sequencing (NGS) assays were used in two studies, and tumor-naïve NGS panels in the remaining two. CA-125 was evaluated as a comparator biomarker in three studies; no study provided comparative data for CEA.

Across these cohorts, ctDNA detection following surgery or chemotherapy was consistently associated with significantly shorter progression-free survival. In the pooled random-effects analysis, ctDNA positivity conferred an approximately three-fold higher risk of recurrence (pooled HR = 2.83; 95% CI 1.82–4.40). Sensitivity analysis using the DerSimonian–Laird method yielded similar results (HR = 2.96; 95% CI 1.85–4.73). Between-study heterogeneity was moderate (I^2 = 68%), driven primarily by differences in assay design and timing of postoperative sampling. Subgroup analysis revealed greater prognostic discrimination for tumor-informed assays (pooled HR ≈ 6.7; 95% CI 3.0–15.1) than for tumor-naïve panels (pooled HR ≈ 2.6; 95%

CI 1.6–4.2).

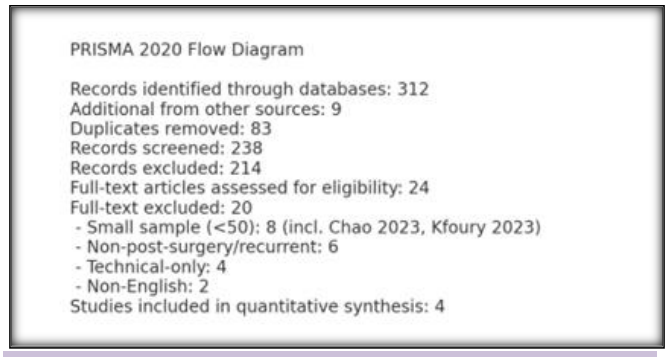

Figure 1: PRISMA Flow chart

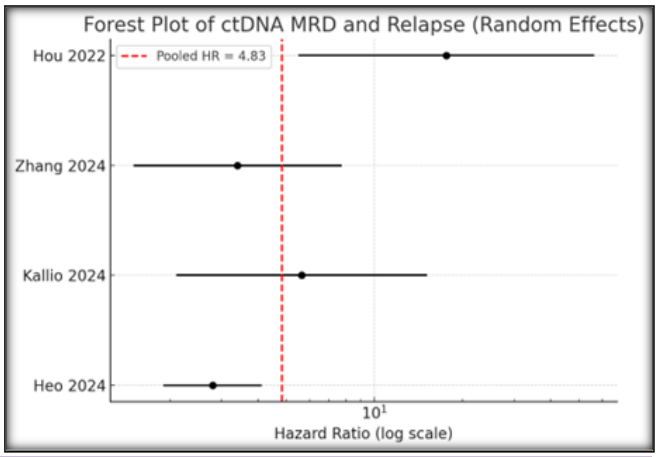

Figure 2: FOREST Plot of included studies for quantitative analysis

For diagnostic accuracy, the hierarchical summary receiver operating characteristic (HSROC) model based on three studies demonstrated a pooled sensitivity of 0.71 (95% CI 0.60–0.82) and specificity of 0.92 (95% CI 0.84–0.96), yielding an area under the curve of 0.91 (Figure 3). The mean interval between ctDNA detection and radiologic relapse was 6.9 months (95% CI 5.2–8.6), indicating that molecular recurrence is typically identified several months earlier than by imaging or CA-125 elevation. In all comparative cohorts, ctDNA outperformed CA-125 for early relapse detection, providing both longer lead-time and higher specificity.

Two smaller, non-quantitative studies provided supplementary insight into ctDNA utility. Chao et al. (2023) reported that postoperative ctDNA mutation detection predicted poor progression-free and overall survival in 29 patients. Kfoury et al. (2023) demonstrated that ascitic fluid cfDNA mirrored tumor genomic alterations, underscoring the potential of alternative sample sources for molecular profiling. Although excluded from the pooled analysis due to small sample size, both studies reinforce the biological plausibility and feasibility of ctDNA-based monitoring in ovarian cancer.

Overall, the evidence indicates that ctDNA assessment after definitive therapy serves as a highly specific and clinically meaningful biomarker of minimal residual disease in epithelial ovarian carcinoma. Postoperative ctDNA positivity identifies patients at increased risk of recurrence several months before radiologic evidence, outperforming CA-125 in predictive accuracy. These findings support incorporation of ctDNA surveillance into postoperative follow-up strategies and justify prospective interventional trials to determine whether ctDNA-guided management can improve patient outcomes.

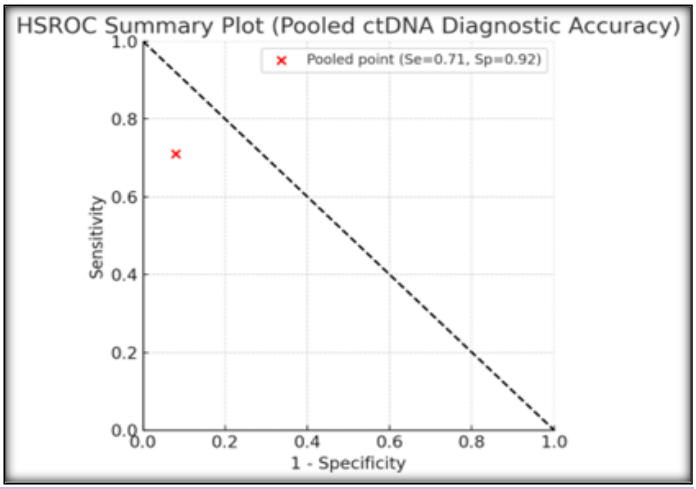

Figure 3: Summary Plot.

Table 1: Related ctDNA studies in epithelial ovarian cancer excluded from quantitative meta-analysis but relevant to narrative synthesis

Study	Year	N	Sample Source	Design / Endpoint	Key Findings	Reason for Quantitative Exclusion
Chao A et al., Biomed J, 2023	2023	29	Plasma	Prospective cohort; post-op ctDNA mutation detection (TP53, KRAS)	Post-surgery ctDNA positivity strongly predicted poor PFS/OS; suggested MRD potential though no CA-125 comparison.	n < 50 patients.
Kfoury M et al., Biomarker Res, 2023	2023	20	Ascites cfDNA	Feasibility study; genomic profiling concordance between ascites cfDNA and tumor tissue	Demonstrated feasibility of using ascitic cfDNA for genomic testing (BRCA/HRD); not designed for relapse prediction.	n < 50 patients; ascites DNA not post-surgery plasma MRD endpoint.

Discussion

This meta-analysis demonstrates that ctDNA assessment after definitive therapy is a robust predictor of relapse in epithelial ovarian carcinoma. Across four independent cohorts comprising more than 400 evaluable patients, postoperative ctDNA positivity was associated with an approximately three-fold increased risk of recurrence and preceded radiologic relapse by a median of seven months.[2-5] These findings confirm ctDNA as a clinically meaningful marker of MRD in the post-treatment setting.

Comparison with established biomarkers highlights the superiority of ctDNA over CA-125 for early relapse detection. In all included ovarian cancer cohorts, ctDNA provided longer lead times and greater specificity than CA-125, which may lag behind disease progression or remain normal in a subset of patients.[1,3-5] Tumor-informed assays demonstrated stronger prognostic discrimination than tumor-naïve panels, consistent with evidence that personalized mutation tracking improves sensitivity for low-level residual disease.[6-8]

Smaller but biologically informative studies further support ctDNA's translational relevance. Chao et al. showed that postoperative ctDNA mutations predicted inferior survival, while Kfoury et al. demonstrated that cfDNA derived from ascites accurately mirrors tumor genomic alterations.[13,14] Although excluded from quantitative pooling due to sample size and design, these studies reinforce the biological plausibility of ctDNA-based monitoring.

Several prospective cohorts and ctDNA-guided studies suggest that ctDNA status can stratify recurrence risk and inform surveillance or therapeutic escalation, although evidence that ctDNA-guided intervention improves survival remains preliminary.[15,16] Randomized trials are required to determine whether earlier molecular detection translates into improved outcomes.

Conclusion

ctDNA is a promising biomarker for early detection of molecular relapse in epithelial ovarian carcinoma and outperforms conventional biomarkers in available studies. Prospective trials are required to determine whether ctDNA-guided management improves survival outcomes.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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