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Role of circulating tumor DNA in early-stage triple-negative breast cancer: a systematic review and meta-analysis

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Abstract

Background Triple-negative breast cancer (TNBC) accounts for 15% of all breast cancers and carries a worse prognosis relative to other breast cancer subtypes. This systematic review and meta-analysis evaluated the prognostic value of circulating tumor DNA (ctDNA) in early-stage TNBC.

Methods A literature search was conducted using Ovid Medline, Elsevier EMBASE, Cochrane Central Register of Controlled Trials, and Web of Science Databases for publications up to 11/16/2023. Results were uploaded to Covidence and assessed by two independent reviewers. Studies assessing the use of ctDNA to predict recurrence free survival and related outcomes as well as overall survival were included. All recurrence outcomes were combined during analysis. Statistical analysis was performed using Revman Web. Log-hazard ratios (HR) were pooled for studies reporting recurrence and death as a time-to-event outcomes. Odds ratios (OR) were calculated and pooled for studies reporting patient-level data on recurrence, death, and pathological complete response (pCR). Prospero ID: CRD42023492529.

Results A total of 3,526 publications were identified through our literature search, and 20 publications ($n=1202$ patients) were included in the meta-analysis. In studies that reported recurrence as a time-to-event outcome, post-neoadjuvant (before or after surgery) ctDNA + status was associated with a higher likelihood of disease recurrence (HR 4.12, 95% confidence interval [CI] 2.81–6.04). For studies that reported patient-level data, post-neoadjuvant ctDNA + status was associated with higher odds of disease recurrence (OR 6.72, 95% CI 3.61–12.54). Pooled log-HR also revealed that ctDNA + status in the post-neoadjuvant setting (before or after surgery) was associated with worse overall survival (HR 3.26, 95% CI 1.88–5.63).

Conclusions Our findings suggest that ctDNA could be used as a prognostic biomarker to anticipate the risk of relapse. However, it remains unclear if therapeutic intervention for patients who are ctDNA + can improve outcomes. While more studies are needed before incorporating ctDNA into clinical practice, the findings of this meta-analysis are reassuring and show the promise of ctDNA as a biomarker.

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Keywords Circulating tumor DNA, Triple-negative breast cancer, Prognosis, Recurrence-free survival, Disease free survival, Overall survival, Post-neoadjuvant, Pathological complete response

Background

Breast cancer is the most common cancer diagnosed in women and the second leading cause of cancer-related mortality in women in the United States [1]. Triple-negative breast cancer (TNBC) is characterized by a lack of hormone receptor expression and non-amplified human epidermal growth factor receptor 2 (HER2). TNBC accounts for 15% of all breast cancers and carries a worse prognosis and the highest risk of recurrence relative to other breast cancer subtypes [2]. Efforts are ongoing to identify novel biomarkers to stratify the risk of recurrence and to optimize the utilization of neoadjuvant and adjuvant therapies.

Both normal and tumor cells release fragments of DNA, known as cell-free DNA (cfDNA), into the bloodstream. Circulating tumor DNA (ctDNA) refers to the portion of cfDNA originating from the tumor cells. The origin of ctDNA is thought to be the cellular breakdown of the tumor through apoptosis, necrosis, and/or phagocytosis, and it offers a relatively non-invasive way to access tumor information [3]. While there is no established standard assay for ctDNA assessment, commonly used techniques to analyze ctDNA involve next-generation sequencing (NGS) or polymerase chain reaction (PCR). These approaches typically require higher tumor content than the commonly identified in patients with early breast cancer. Thus, new assays have been developed to detect very low ctDNA levels in early breast cancer. These can be categorized as tumor-informed, where tumor tissue is sequenced and an individualized ctDNA assay is produced for each patient based on identified mutations, or tumor-agnostic, which utilizes characteristic genomic, epigenomic and/or fragmentomic patterns to identify ctDNA and does not require prior knowledge of tumor-related mutations.

ctDNA has shown promise as a prognostic marker in early breast cancer and other tumor types [3]. Detectable ctDNA after curative-intent therapy is called molecular (or minimal) residual disease (MRD) [4–6]. For example, in colorectal cancer, Reinart et al. showed that in patients with stage I to III colorectal carcinoma, those with ctDNA + status at post-operative day 30 were seven times more likely to relapse than patients with ctDNA- status, suggesting that ctDNA may have value in solid tumors as a method of risk stratification or early relapse detection [6]. ctDNA + status has been associated with a high risk of recurrence in breast cancer. For example, in the phase II adjuvant OXEL trial, patients with TNBC with residual disease after neoadjuvant chemotherapy were randomized to capecitabine, an immune checkpoint inhibitor, or the combination. Those with detectable ctDNA after neoadjuvant therapy and surgery were more likely to relapse [7]. Even though the use of ctDNA is an area of significant interest in breast cancer, its clinical use remains limited as most of the data is based on small, retrospective studies in which ctDNA is not the primary endpoint.

The main objective of this study was to evaluate the correlation between ctDNA detection and long-term outcomes such as disease recurrence and survival. We were most interested in ctDNA detection at the post-neoadjuvant timepoint (before or after surgery) as it can potentially influence treatment decisions. Potential applications of ctDNA include personalization of therapies, giving more aggressive and potentially personalized treatments for those likely to have worse outcomes, de-escalating regimens for patients who are likely to have better outcomes along with optimizing long-term outcomes and aiming to minimize toxicities.

Materials and methods

Search strategy and study selection

A literature search was conducted using online databases Ovid MEDLINE, Elsevier Embase, Cochrane Central Register of Controlled Trials, and Web of Science. A combination of subject headings and keyword search terms were used for "Circulating Tumor DNA," "DNA, Neoplasm," "Triple Negative Breast Neoplasms," "Prognosis," "Risk," and "Survival Analysis." All English publications available through November 16, 2023 were retrieved without any restriction on country of origin or study population. A more detailed search strategy is available in supplementary Table 1. The study protocol was registered with PROSPERO (International Prospective Register of Systematic reviews, ID: CRD42023492529).

Records retrieved were imported into the COVIDENCE software (Veritas Health Innovation, Melbourne, Australia. Available at www.covidence.org.), and duplicates were removed. Six investigators (DZ, FS, JD, XH, CW, PT) were involved in study screening and selection. Two investigators independently screened each abstract for inclusion. Researchers were blinded to each other's decisions. In case of disagreement, a third investigator was consulted for the final decision (DZ, IS). The full-text review was performed following the same protocol. To determine inter-rater reliability, Cohen's kappa (K) was calculated. For abstract screening, the highest K = 0.81, for full text screening, the highest K = 0.78.

The inclusion criteria to be included in the present study were: (1) Papers of observational studies (prospective or retrospective) or randomized control trials;

(2) Papers that include patients with early-stage (non-metastatic) TNBC treated with curative intent (the study can include patients with other breast cancer subtypes; however, outcome information specific for patients with TNBC must have been available); (3) Have documentation of ctDNA in blood samples (any method of ctDNA detection and analysis was accepted); (4) Include long term outcome data on survival and recurrence must be available.

Exclusion criteria included: (1) Papers with patients with metastatic breast cancer or other breast cancer subtypes; (2) Patients with other types of cancer; (3) Studies using liquid biopsy methods other than ctDNA (such as circulating tumor cells); (4) Studies that did not report patient outcomes; (5) Preclinical studies.

Data extraction

Data extraction was performed by a single investigator (DZ). When available, data extracted included: (1) Study characteristics (including author, year of publication, publication type, study design, and phase); (2) Patient characteristics (including sample size, age, race, tumor characteristics, treatment received); (3) ctDNA detection and analysis method (including timepoints of ctDNA assessment, type of assay used, whether or not it was informed by sequencing of the primary tumor); (4) Long term outcomes related to death and recurrence; (5) The rate of pathological complete response (pCR); (6) lead time between ctDNA detection and disease recurrence. Recurrence outcomes were defined by STEEP criteria [8] and included disease-free survival (DFS), distant disease-free survival (DDFS), invasive disease-free survival (IDFS), recurrence-free survival (RFS), distant recurrence-free survival (DRFS), event-free survival (EFS), recurrence-free interval (RFI), and recurrence rate. Survival outcomes included overall survival (OS) and number of death events. Timepoints of ctDNA assessment included baseline (before any treatment), during neoadjuvant therapy, post-neoadjuvant therapy (both before or after surgery), and during or after adjuvant therapy.

Risk of bias and quality assessment

Risk of bias was assessed using the Quality in Prognostic Studies (QUIPS) tool [9]. Quality was assessed using tools from the National Heart, Lung, and Blood Institute (NHLBI) [10]. Three investigators (DZ, FS, JD) were involved in assessing study bias and quality. Each included study was assessed independently by two investigators, and disagreements were resolved through discussion. Full risk of bias and quality assessment information is available in supplemental Table 2.

Statistical analysis

Statistical analysis was performed using Revman Web. For studies that reported survival and recurrence as time-to-event outcomes, log-hazard ratios (log-HRs) were pooled using a random effects model with an inverse variance test and reported as HR with 95% confidence intervals (95%CI). For this meta-analysis, all recurrence outcomes that were collected during data extraction were analyzed together.

For some studies, particularly those with smaller sample sizes that reported patient-level data on recurrence rate and achievement of pCR, we performed a separate analysis using a Mantel-Haenzel test and reported as an odds ratio (OR) with a 95%CI. Pvalues < 0.05 and were considered significant. We contacted the authors directly for any missing outcomes and included additional information if it was provided.

Of note, the Cavallone 2020 and Roseshter 2023 studies reported HR for non-recurrence, while other studies reported HR for recurrence. After confirming with the original authors, we took the reciprocal of their reported HRs for inclusion in this analysis.

Assessment of heterogeneity

In the meta-analysis, we included only those comparisons and outcomes for which we had two or more data points. Fixed and random-effect models were employed to evaluate the homogeneity of trials combined in the meta-analysis. The extent of heterogeneity regarding the association between ctDNA detection and disease outcomes was measured by Cochrane's Q, which was calculated as a weighted sum of the squared differences between individual and pooled effects across studies. The alpha level was set at 0.10, recognizing that the chi-square test for heterogeneity is a low-power test. The magnitude of heterogeneity was then assessed using the I^2 score, and any score equal to or above 40% was investigated using subgroup and sensitivity analysis.

Subgroup analysis and sensitivity analysis

In the present study, subgroup analysis was performed to examine the impact of several variables where feasible, including the timing of post-neoadjuvant ctDNA evaluation (before or after surgery), whether ctDNA measurement was tumor-informed, and the timing and type of treatment received. Furthermore, sensitivity analysis was carried out to evaluate the robustness of the results by testing their dependence on the study quality. This was accomplished by systematically excluding each study from the analysis.

Results

Study characteristics

A total of 3,526 publications were identified through our literature search, and 20 publications ($n = 1202$ patients) were included in the meta-analysis. The PRISMA diagram of the screening process is shown in Fig. 1. Out of the included studies, there were ten prospective observational studies ($n = 409$), nine clinical trials ($n = 751$), and one prospective case-control study ($n = 42$). Most of the studies were retrospectively analyzed. Tumor-informed assays were used by 13 studies ($n = 774$), while six used tumor-agnostic assays ($n = 392$), and one did not specify assay type ($n = 36$). ctDNA analysis was done using PCR in seven studies ($n = 513$) and NGS in 13 ($n = 689$).

In terms of treatment, six ($n = 300$) studies included patients who received neoadjuvant therapy, while 13 ($n = 866$) included patients who received both neoadjuvant and adjuvant therapy. In 13 studies ($n = 629$) patients received chemotherapy only, and in six ($n = 537$) patients received chemotherapy and a different, often investigational, treatment. One study ($n = 38$) did not specify treatment details. Detailed study characteristics are described in Table 1. We focused on results based on ctDNA detection either during/post-neoadjuvant therapy, or during/after adjuvant therapy. Even though several of the included studies included reported results on baseline ctDNA, there was not enough data to include in the meta-analysis. Some studies reported ctDNA assessment in follow-up (after completion of all treatment) and correlation with DFS or OS, however the definitions of follow-up time frames were heterogeneous, and we were not able to combine the data in a meaningful way.

Correlation between ctDNA detection and recurrence

We pooled log-hazard ratios using a random effects model with an inverse variance test for nine studies ($n = 752$) that reported recurrence as a time-to-event outcome. This showed that post-neoadjuvant ctDNA + status (both before and after surgery) was associated with a higher likelihood of disease recurrence [Fig. 2, HR 4.12, 95% confidence interval (CI) 2.81–6.04]. The test of overall effect was significant ($z = 7.23$, $p < 0.00001$), suggesting that ctDNA + status is a marker of a worse prognosis.

Subgroup analysis was performed to evaluate heterogeneity between the studies ($Chi^2 = 12.18$, $I^2 = 34\%$). Separating studies with ctDNA samples drawn before surgery and those drawn after surgery (figure S1) did not significantly impact the results. However, there was heterogeneity in the studies with post-surgical ctDNA samples ($Chi^2 = 10.82$, $I^2 = 63\%$) and no heterogeneity between studies where ctDNA was drawn before surgery ($Chi^2 = 1.28$, $I^2 = 0\%$). Subgroup analysis also showed that studies utilizing tumor-informed assays had no heterogeneity ($Chi^2 = 1.31$, $I^2 = 0\%$) and a stronger overall effect (figure S2, HR 4.2, 95% CI 2.93–6.03), which suggests they may have more accuracy than tumor agnostic assays (figure S2, $Chi^2 = 6.86$, $I^2 = 71\%$, HR 4.52, 95%CI 1.41–14.47). Further subgroup analyses separating studies by

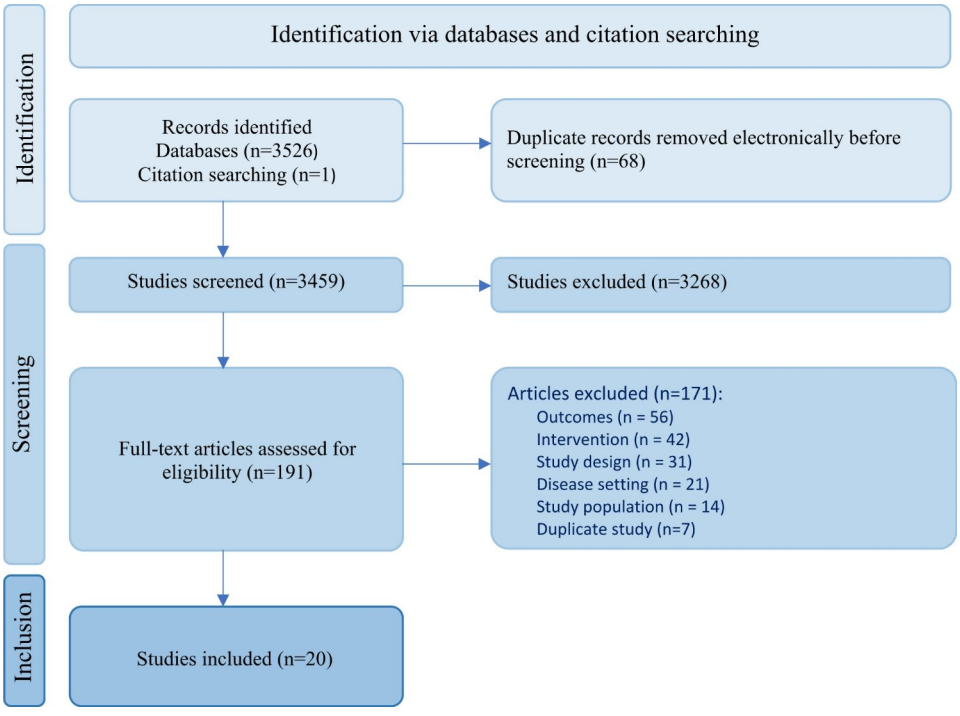

Fig. 1 PRISMA flow diagram

Table 1 Study characteristics

Study	Study type	Phase	Total evaluable for ctDNA *N*= (TNBC *n*=)	Disease stage	ctDNA analysis method	ctDNA time points	Outcomes	Median follow-up
Barnell 2022 [20]	Single arm, open label	II	50 (50)	II-III	Personalized PCR panel (4–6 variants) based on tumor WES	Baseline, during NACT (C1D3), post-NACT (at surgery), every 6 m for 5 years, at relapse	Relationship of ctDNA to recurrence outcomes and pCR	Up to 48 months
Butler 2019 [21]	Open label, multi-center adaptive randomized platform trial (I-SPY 2)	II	10 (3)	II-III (cT1-4, N0-1)	DIDA unique molecular identifier sequencing based on tumor WES	Baseline, before every cycle of NACT, post-NACT (before surgery), after surgery, every 6 months after	Whether ctDNA levels and composition can predict response to treatment	Not specified
Cailleux 2022 [22]	Prospective, translational		44 (13)	cT1-4, cN0-1	Personalized NGS (Signatera, up to 16 mutations) based on tumor WES	Baseline, post-NACT (before surgery), various unspecified follow-up times	EFS	3.03 years (0.39–5.85 years)
Cavallone 2020 [13]	Prospective, observational		26 (26)	II-III (cT0-4, N0-3)	Personalized PCR panel (average 5 variants) based on tumor WES	Baseline, during NACT (3 timepoints), post-NACT (before surgery), 10 patients drawn after surgery	RFS, OS	63 months
Chen 2017 [23]	Open label, multi-site, randomized (BRE09-146)	II	38 (38)	I-III	NGS (Ion Ampliseq Oncomine), matched tumor and plasma mutations	During adjuvant (C1 and C2 of adjuvant cisplatin + rucaparib, during maintenance (weeks 1 and 5 of maintenance rucaparib)	DFS	24 months
Chen 2020 [24]	Observational		36 (36)	Early and metastatic	NGS (Roche Avenio), unclear if tumor informed	First day of adjuvant intervention	DFS, lead time interval	Not specified
Gupta 2023 [25]	Single arm, open label	II	29 (29)	I-III	Personalized NGS (Signatera, up to 16 mutations) based on tumor WES	Before, during, and after adjuvant capecitabine	ctDNA detection and correlation with tumor genomics, RFS, OS	19.3 months (10.7–43.7)
Lee 2023 [26]	Prospective, observational		11 (11)	cT2-3, N2-3	NGS, non-tumor informed	Before radiation, 3 weeks after radiation, and 1 month after radiation	DFS	48 months
Lin 2021 [27]	Prospective, observational		95 (25)	II-III	NGS, non-tumor informed	Baseline, post-NACT (after surgery)	RFS	5.1 years
Magbanua 2023 [12]	Open label, multi-center adaptive randomized platform trial (I-SPY 2)	II	283 (138)	II-III (cT1-4, N+/-)	Personalized NGS (Signatera, up to 16 mutations) based on tumor WES	Baseline, during NACT (at 3 weeks and 12 weeks), post-NACT (before surgery)	pCR, DRFS	3.12 years (0.31–7.91)
Molinero 2022 [28]	International, multicenter, open label, 2 arm	III	186 (186)	"early", stage not specified	Personalized assays (up to 16 SNVs) based on tumor WES	After surgery before ACT, post-ACT	IDFS, OS	Not specified
Ortolan 2021 [29]	Prospective, observational		31 (31)	II-III (cT2-4, N+/-)	Personalized PCR assay (1 mutation) based on tumor NGS	Baseline, during NACT, after NACT (before surgery), after surgery	EFS	3 years (0.5–6.5)

Table 1 (continued)

Study	Study type	Phase	Total evaluable for ctDNA *N*= (TNBC *n*=)	Disease stage	ctDNA analysis method	ctDNA time points	Outcomes	Median follow-up
Parsons 2023 [30]	Case-control subset of a prospective, randomized trial (TBCRC 030)	II	42 (42)	cT1-3, N+/-	ctDNA assays (up to 1000 mutations per patient) based on tumor WGS	Baseline, 3 weeks into NACT, at 12 weeks of NACT (before surgery)	ctDNA dynamics in relation to tumor response and disease recurrence	Not specified
Radovich 2020 [31]	Multicenter, randomized control trial (BRE12-158)	II	142 (142)	I-III	NGS (Foundation), non-tumor informed	Before ACT (after surgery and radiation)	DDFS	17.2 months (0.1–58.3 months)
Roseshter 2023 [32]	Prospective, observational		34 (34)	Not specified	Personalized PCR assay (5 mutations) based on tumor WES	Post-NACT (before surgery), after surgery, 3 months (during ACT), 6 months (after ACT)	RFS	Not specified
Schneider 2022 [33]	Multicenter, randomized control trial (BRE12-158)	II	146 (146)	I-III	NGS (Foundation), non-tumor informed	T0 = after surgery, before adjuvant treatment	DDFS, DFS, OS	34.2 months
Shaw 2024 [34]	Multicenter, prospective, observational		153 (23)	I-III	Personalized NGS (Signatera, up to 16 mutations) based on tumor WES	Every 6 months for up to 4 years in patients that completed therapy in the past 3 years	RFS, OS	58 months (8–99)
Stecklein 2023 [35]	Multicenter, prospective, observational		80 (80)	I-III	NGS, non-tumor informed	1–6 months after all treatment (local and systemic)	EFS	31 months
Turner 2023 [36]	Multicenter, prospective clinical trial (c-TRAK)	II	161 (161)	II-III	Personalized PCR (1–2 mutations) based on tumor NGS	After all treatment, then every 3 months for 24 months	ctDNA detection and clearance rate	20.4 months
Zaikova 2024 [37]	Prospective, observational		130 (130)	cT1-4, N+/-	NGS, non-tumor informed	Within 7 months after completion of all therapy	RFS	25 months (1–53)

ACT: Adjuvant chemotherapy; NACT: Neoadjuvant chemotherapy; DIDA: Dual-Indexed Degenerate Adapter; WES: Whole exome sequencing; NGS: Next generation sequencing, PCR: Polymerase chain reaction; EFS: Event-free survival; RFS: Recurrence-free survival; OS: Overall survival; DFS: Disease-free survival; DDFS: Distant disease-free survival; IDFS: Invasive disease-free survival; DRFS: Distant recurrence-free survival; pCR: Pathological complete response

timing and type of treatment are available in the supplemental material figures S3-4.

For nine studies with smaller sample sizes ($n = 315$) that reported patient-level data on ctDNA and recurrence events, we performed a separate analysis using a fixed effect model with the Mantel-Haenzel test, which showed that post-neoadjuvant ctDNA + status was associated with higher odds of disease recurrence (Fig. 3, OR 6.72, 95%CI 3.61–12.54). The test of overall effect was significant ($z = 5.99$, $p < 0.00001$), and heterogeneity between the study results was low ($Chi^2 = 6.34$; $I^2 = 0\%$). Risk of bias assessment using the QUIPS tool suggested low risk of bias for most studies. Chen 2020 and Butler 2019 had several high points for the risk of bias. Moreover, Butler 2019 and Lee 2023 reported zero recurrence events in the ctDNA- arm, which could lead to a higher risk for bias favoring the ctDNA + group. Therefore, we conducted a sensitivity analysis where the aforementioned studies were excluded, which overall showed no significant difference in the main effect of the forest plot (figure S8A). We also removed from the analysis the study with a high risk of bias (Chen 2020) and noted an approximately 20% reduction in the odds of ctDNA positivity in the post-neoadjuvant setting being associated with a higher risk of recurrence; however, the correlation was still strong (figure S8B, HR 5.38, 95% CI 2.79–10.40).

A subgroup analysis separating studies where ctDNA was drawn before surgery versus those where ctDNA was drawn after surgery did not have a significant impact on the main result of the plot (figure S5). However, there was more heterogeneity in the "after surgery" group. Other subgroup analysis comparing studies that used tumor informed versus tumor agnostic ctDNA assays did not have a significant impact on the results or heterogeneity

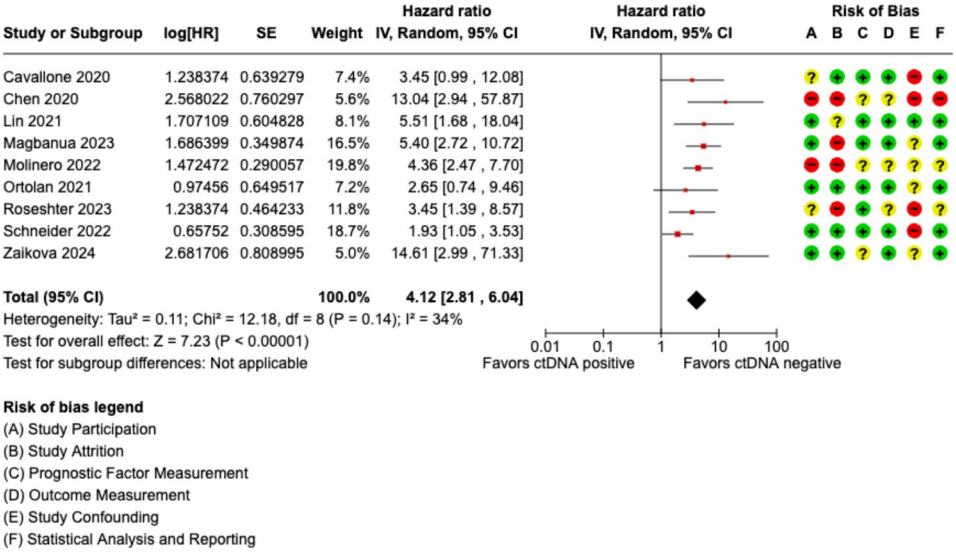

Fig. 2 Correlation between ctDNA detection in the post-neoadjuvant setting (before or after surgery) for studies reporting recurrence as a time-to-event outcome. Risk of bias legend in this figure applies as well to Figs. 3 and 4 and S1-13
CI: Confidence interval; HR: Hazard ratio; IV: Inverse variance; SE: Standard error

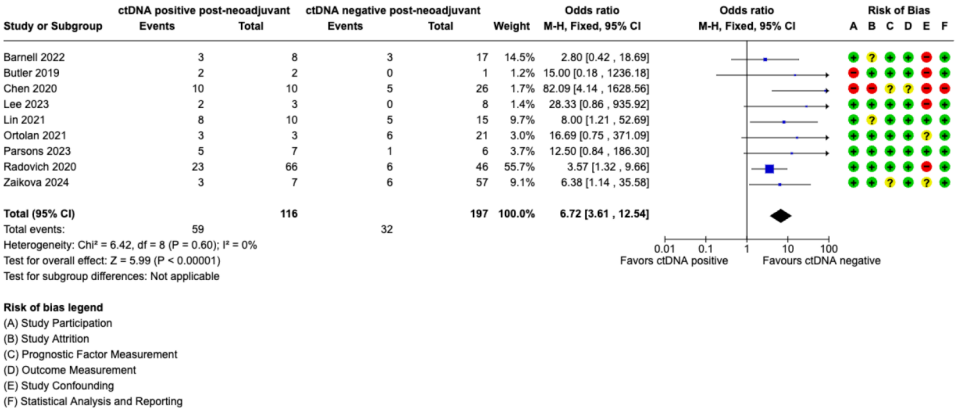

Fig. 3 Correlation between ctDNA detection in the post-neoadjuvant setting (before or after surgery) with patient-level recurrence data
M-H: Mantel-Haenzel; CI: Confidence interval

of the plot (figure S6). Most studies shown in this section received neoadjuvant and/or adjuvant chemotherapy, while patients in Radovich 2020 were randomized to receive genomically directed adjuvant therapy or physician's choice therapy. The subgroup of studies who received neoadjuvant treatment alone showed higher odds of ctDNA + being associated with disease recurrence. However, they also had small patient populations with wide confidence intervals; therefore, these results should be interpreted with caution (figure S7).

Four studies ($n = 338$) reported recurrence as a time-to-event outcome concerning ctDNA + status during or after adjuvant therapy. A random effects model with an inverse variance test showed that ctDNA + status at this time point was associated with a higher likelihood of disease recurrence (figure S9, HR 7.51, 95%CI 4.80-11.74). The test of overall effect was statistically significant (z = 8.85, $p < 0.00001$), and there was no heterogeneity between study results ($Chi^2 = 1.75$, $I^2 = 0\%$).

There were fewer studies that reported on ctDNA detection at other timepoints such as at baseline (prior to neoadjuvant therapy) or during neoadjuvant therapy. While we did not have enough data to combine in analysis, overall pattern suggests that testing ctDNA + during neoadjuvant chemotherapy is correlated with higher likelihood of recurrence. Riva et al. reported out of 35 early-stage TNBC patients, 4/4 patients who experienced distant metastatic recurrence tested ctDNA + after their first cycle of neoadjuvant chemotherapy. Occurrence of metastatic relapse was significantly correlated with ctDNA positivity after 1 cycle of treatment ($p = 0.002$) [11]. Similarly, Per Magbanua et al., in a cohort of TNBC patients who remained ctDNA + three weeks into neoadjuvant therapy (85/128), ctDNA detection was correlated

with worse DRFS (HR 3.00, 95%CI 1.32–6.80, $p = 0.0055$) [12]. Per Cavallone et al., in TNBC patients who tested positive for ctDNA after one cycle of neoadjuvant chemotherapy (17/24), there was a trend towards correlation with worse RFS that was not statistically significant (HR 3.125, 95%CI 0.9–11.1) [13]. Therefore, slower clearance of ctDNA during neoadjuvant chemotherapy could be associated with higher risk disease and increased risk of recurrence. As described previously, the reciprocal of the published HR was taken for the Cavallone et al. study for comparison purposes.

Correlation between ctDNA positive status and overall survival

For three studies ($n = 358$) that reported death as a time-to-event outcome, a random effects model with an inverse variance test showed that positive ctDNA status in the post-neoadjuvant setting was associated with worse overall survival (figure S10, HR 3.26, 95%CI 1.88–5.63). Test of overall effect was statistically significant ($z = 4.23$, $p < 0.0001$) and we found no heterogeneity between the study results ($Chi^2 = 0.50$, $I^2 = 0\%$). The only study where samples were drawn before surgery was Cavallone 2020. The studies were combined since the results were homogenous.

A random effects model with an inverse variance test showed that positive ctDNA status during or post-adjuvant therapy (two studies, $n = 266$) was associated with worse overall survival (figure S11, HR 7.96, 95%CI 1.59–39.78). The test of the overall effect was significant ($z = 2.53$, $p = 0.01$). We found significant heterogeneity ($Chi^2 = 5.91$ $I^2 = 83\%$) due to the low number of studies included in this analysis; therefore, results should be interpreted with caution.

Correlation between ctDNA positive status and pathologic complete response

For three studies ($n = 132$) that reported patient-level data on ctDNA and pathologic complete response (pCR), a random effects model with a Mantel-Haenzel test showed that it was less likely for those with positive ctDNA status during neoadjuvant therapy to exhibit a pCR (figure S12, OR 0.16, 95%CI 0.06–0.41). The test of overall effect was significant ($z = 3.81$, $p = 0.0001$), with low heterogeneity found between study results ($Chi^2 = 2.15$; $I^2 = 7\%$).

A random effects model with a Mantel-Haenzel test showed that it was less likely for those with positive post-neoadjuvant ctDNA status to achieve a pCR [(Fig. 4, OR 0.22, 95%CI 0.04–1.05); seven studies, $n = 211$]. Test of overall effect approached significance ($z = 1.9$, $p = 0.06$). Since there was heterogeneity between the results ($Chi^2 = 16.94$; $I^2 = 59\%$), we performed a sensitivity analysis where we removed the study by Ortolan et al. for zero events in the ctDNA negative status arm, which could bias the results towards the ctDNA positive status arm. This reduced the heterogeneity to 0% and changed the OR to 0.12 (95%CI 0.04–0.36, figure S13).

Lead time between ctDNA detection and disease recurrence

There were seven studies including data from ($n = 553$) patients that reported on lead time between initial ctDNA detection and diagnosis of clinical/radiographic recurrence. Table 2 summarizes the median lead times and the time ctDNA was drawn. Most studies use ctDNA drawn either during or after adjuvant treatment (4/7 studies), while 3/7 evaluate ctDNA drawn after all treatment (including radiation, if it was indicated). In these cases, the median lead time between initial ctDNA detection and occurrence of clinical recurrence is short, many less than six months, and all under 12 months. It should be noted that four of these studies (Gupta 2023, Stecklein 2023, Shaw 2024, and Chen 2017) included only patients who did not experienced a pCR, while Turner 2023 included patients with either residual disease after neoadjuvant treatment or tumor size > 20 mm and/or axillary lymph node involvement with primary surgery. These represent patient populations who are known to

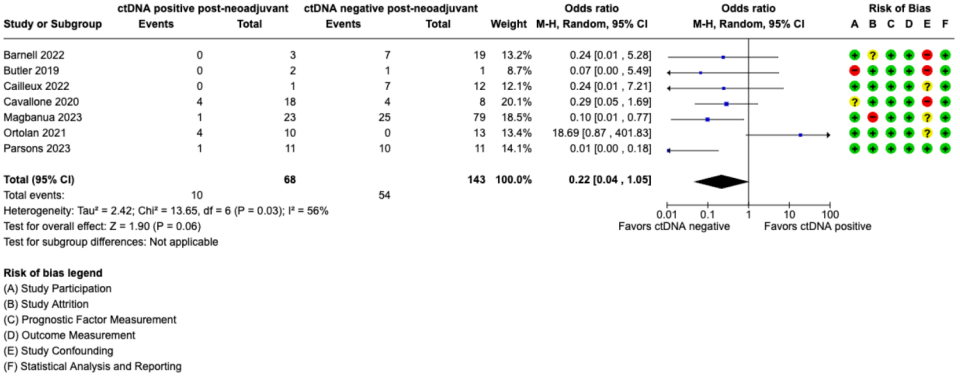

Fig. 4 Correlation between ctDNA detection in the post-neoadjuvant setting (before surgery) with patient-level data on achievement of pCR
M-H: Mantel-Haenzel; CI: Confidence interval

Table 2 Lead time between first ctDNA detection and clinical disease recurrence

Study	Median lead time (months)	Lead time range (months)	ctDNA testing time
Molinero 2022 [28]	6.1	0-30.5	After adjuvant
Gupta 2023 [25]	3.85	0.6–11	After adjuvant
Stecklein 2023 [35]	4.7	Not reported	After all treatment
Turner 2023 [36] (observation arm)*	4.1	Not reported	After all treatment*
Turner 2023 [36)] (intervention arm)*	1.6	Not reported	After all treatment*
Shaw 2024 [34]	8	0–19	After all treatment
Chen 2017 [23]	4.2	0.07–8.87	During adjuvant
Chen 2020 [24]	Not reported	0.07–20.93	First day of adjuvant

* Prospective study where patients where ctDNA positive patients were allocated to an intervention arm (pembrolizumab) or observation arm. Initially ctDNA testing started after all treatment. After August 6 2019 amendment (154/208 patients were already enrolled), ctDNA testing started before or during radiotherapy

be at high risk for relapse. ctDNA may, therefore, have more value if drawn earlier in the treatment process to give more time for potential intervention, as those who have detectable ctDNA in the adjuvant or follow-up setting tend to have short intervals to recurrence.

Discussion

In this systematic review and meta-analysis, we found that ctDNA detection in the post-neoadjuvant setting, both before and after surgery, is associated with a higher risk of disease recurrence and worse OS. Similarly, ctDNA detection during or after adjuvant therapy is associated with a higher risk of disease recurrence and overall survival. These findings suggest ctDNA detection is a negative prognostic biomarker in early TNBC. These findings are consistent to prior studies, to our knowledge, this is the first time this data has been systematically analyzed for early TNBC.

Other studies have assessed the role of ctDNA across all breast cancer subtypes. A recent meta-analysis performed by Nader-Marta et al. revealed that ctDNA detection at baseline before treatment, after neoadjuvant therapy, and during follow-up was associated with worse disease-free interval and OS across all breast cancer subtypes [14]. However, we decided to focus on TNBC as this subtype has the highest risk of recurrence; therefore, identifying a biomarker that can predict recurrence is valuable and could eventually influence treatment decisions.

Furthermore, narrowing down a single subtype allows us to identify the optimal timing of ctDNA assessment, which can be challenging when other subtypes are included, as perioperative management differs between them, as well as median time to relapse. In this case, the post-neoadjuvant time point for ctDNA assessment appears to be a prognostic biomarker. Based on the studies in this meta-analysis, the lead time between ctDNA detection and clinical disease recurrence is short when ctDNA is tested in the adjuvant or post-treatment setting, particularly in high-risk patient populations. Therefore, earlier testing, either immediately before or soon after surgery, may give more opportunity for intervention.

Even though this study showed that ctDNA detection before and after surgery correlated with an increased risk of recurrence, these are two district scenarios. Our study revealed that pCR is less likely if ctDNA is detected during neoadjuvant treatment or before surgery. Therefore, ctDNA could be helpful to incorporate into adaptive trial designs where experimental treatments can be escalated or de-escalated based on mid-treatment clinical and radiographical assessments that predict treatment efficacy (as is being done in the I-SPY2 trial, NCT01042379) [15]. Based on Magbanua et al., ctDNA status could also refine the prognostic value of established predictive markers like pCR and residual cancer burden (RCB). In the TNBC cohort who did not achieve pCR, patients with positive post-neoadjuvant ctDNA (before surgery) had higher risk of metastatic recurrence and death than ctDNA-negative status patients (HR 3.84, 95%CI 1.70–8.66). A similar pattern was seen when comparing patients with RCB 0/I versus RCB II/III. TNBC patients who were ctDNA + and RCB II/III had worse DRFS compared to those who were ctDNA- (HR 3.84; 95%CI 1.70–8.66) [12]. More studies evaluating these relationships will need to be done to establish if ctDNA can add value to these existing predictive markers.

Several ongoing trials aim to use ctDNA to guide treatment. The phase II CUPCAKE trial (NCT06225505) is enrolling patients with TNBC who completed all treatment to undergo ctDNA testing every three months and undergo evaluation for metastatic disease with PET-CT and other work-up if positive [16]. Another phase II trial (NCT04768426) is evaluating ctDNA in TNBC patients with residual disease after neoadjuvant chemotherapy who are receiving standard-of-care capecitabine to correlate ctDNA levels with genomic features and survival to potentially identify patients who may benefit from treatment other than capecitabine [17]. The phase II Apollo trial (NCT04501523) is enrolling patients with TNBC who have completed neoadjuvant chemotherapy and surgery to undergo ctDNA testing every three months, and

if positive, be randomized to a 12-month course of tislelizumab (an immune checkpoint inhibitor) or placebo [18]. However, we should take into account that the success of treatment escalation trials also depends on the efficacy of the selected regimen, especially for patients that have been treated with multiple chemotherapies and immune checkpoint inhibition, and not just the biomarker is used to direct treatment.

There are several limitations to our systemic review and meta-analysis. Most of the studies included are observational or an observational subset of a clinical trial and largely retrospectively analyzed. As the trials were not all designed with ctDNA assessment as a primary endpoint, patients were not stratified by baseline characteristics, and confounding factors (such as tumor characteristics, nodal status, treatments received) were not necessarily controlled for during statistical analysis. Some of the studies only included patients who had residual disease, which is known to be a predictor of recurrence. These confounding factors could have influenced the results of this meta-analysis. Additionally, most of these studies recruited patients prior to publication of KEYNOTE-522 and therefore very few received immunotherapy even though it is now considered standard of care in perioperative treatment of TNBC. ctDNA was not collected as part of the KEYNOTE-522 trial; therefore, we do not know how immunotherapy could impact the ctDNA assessment.

The studies included in this meta-analysis also used heterogenous techniques for ctDNA analysis as there is no standardized method at this time. Some studies used PCR-based assays, while others used NGS, some assays were tumor informed, and others were not. The studies also varied widely on the number of variants being followed, which could impact the sensitivity of the results. As this is a rapidly evolving field, newer, more sensitive methods are being developed that could improve the detection of lower ctDNA levels in early-stage disease. For example, Garcia-Murillas et al. studied the ultrasensitive NeXT Personal ctDNA-based MRD platform which used whole exome sequencing of the tumor to produce personalized panels of up to ~1800 variants to test for MRD. When used in 76 patients with early breast cancer (including 23 TNBC), 100% of TNBC patients had detectable ctDNA at baseline prior to therapy. Samples were collected for ctDNA during neoadjuvant therapy, after surgery, and in follow-up (every 3 months for the first year and every 6 months for up to five years). Detection of ctDNA after surgery was associated with a high risk of future relapse and worse OS ($p < 0.0001$; log-rank test) for all subtypes. MRD was positive in 10/10 patients who relapsed, and no patients without detectable ctDNA relapsed during median 76-month follow-up [19]. Also, since ctDNA was reported as positive or negative (binary), there is limited granularity on ctDNA dynamics.

Conclusion

We demonstrated that ctDNA detection post-neoadjuvant therapy, either before or after surgery is correlated with increased risk of recurrence and worse overall survival. We found similar results for ctDNA detection during or after adjuvant therapy. These findings suggest that ctDNA may have a role as a negative prognostic marker in early TNBC.

ctDNA is an exciting topic in precision oncology with many possible uses are on the horizon. It has the potential to be used as an adaptive tool, and to monitor for early evidence of recurrence after therapy. It could also be used to individualize patient care based on specific detected mutations. Further work is being done to determine the clinical significance of ctDNA positivity and whether intervening on a positive test can improve outcomes.

Abbreviations

TNBC	Triple-negative breast cancer
HER2	Non-amplified human epidermal growth factor receptor 2
cfDNA	Cell-free DNA
ctDNA	circulating tumor DNA
NGS	Next-generation sequencing
PCR	Polymerase chain reaction
MRD	Molecular (or minimal) residual disease
PROSPERO	International Prospective Register of Systematic reviews
K	Cohen's kappa
pCR	Pathological complete response
RCB	Residual cancer burden
DFS	Disease-free survival
DDFS	Distant disease-free survival invasive disease-free survival
RFS	Recurrence-free survival
DRFS	Distant recurrence-free survival
EFS	Event-free survival
RFI	Recurrence-free interval
OS	overall survival
QUIPS	Quality in Prognostic Studies
NHLBI	National Heart, Lung, and Blood Institute
HR	hazard ratio
OR	Odds ratio
CI	Confidence interval

Supplementary information

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Supplementary Material 1

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Author contributions

IS conceived the study and is the corresponding author, DZ helped conceive the study and led the study screening, data extraction, statistical analysis, and manuscript writing process, SJ contributed to statistical analysis, JR performed the literature search, JD, FS, CW, XH, and PT performed study screening, AM, MBasik, PHL, CSH, FCB, and SR provided additional information to aid this meta-analysis, LP and MBuss provided direction and feedback, HP provided

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Data availability
Data supporting the findings of this study are available within the paper and supplemental materials. Requests for additional information should be addressed to the corresponding authors.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
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