Editorial

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The cfDNA in early cancer detection

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Cell-free DNA (cfDNA) refers to fragments of DNA circulating freely in the bloodstream and other bodily fluids. The existence of cfDNA was first reported in 1948 by Mandel and Métais, who discovered cell-free nucleic acids in human plasma [1]. However, it was not until the 1970s that cfDNA was confirmed to be of tumor origin, when increased levels were found in cancer patients compared to healthy controls [2]. This circulating tumor DNA (ctDNA) arises from apoptotic and necrotic tumor cells that have released their fragmented DNA into circulation. In the 1990s and 2000s, advancements in sensitive molecular techniques like quantitative PCR and digital PCR enabled the detection and analysis of cfDNA mutations and methylation patterns [3]. This allowed cfDNA to be established as an important biomarker for cancer detection, prognosis, and treatment monitoring. Today, cfDNA analysis continues to be an area of active research, with applications spanning cancer screening, diagnosis, prognosis, therapeutic response monitoring, and resistance mutation detection [3,4].

The ctDNA carries the same genetic and epigenetic alterations as the tumor itself, acting as a surrogate for the molecular profile of the underlying malignancy [5,6]. These tumor-specific changes include point mutations, copy number alterations, methylation abnormalities, and chromosomal rearrangements. The ctDNA enters the bloodstream by various mechanisms, including apoptosis and necrosis of cancer cells, secretion of vesicles, or spontaneous release [7–9]. Once in the circulation, ctDNA can be analyzed by techniques like quantitative PCR, digital PCR, beads-emulsification-amplification-magnetics (BEAMing), and next-generation sequencing [10–14].

Since ctDNA contains the same genetic mutations and epigenetic alterations as the tumor itself, it can serve as a “liquid biopsy” that allows non-invasive analysis and monitoring of cancers. Several studies have shown the potential of using ctDNA for early cancer detection across multiple cancer types. For example, a recent study developed an assay that analyzed the fragment length profiles of cancer mutations in cfDNA to detect hepatocellular carcinoma [15]. The assay could distinguish patients

with early-stage HCC from healthy controls with 81% sensitivity and specificity. Another study showed that integrative modeling of tumor genome and epigenome features enhanced early cancer detection from cfDNA [16]. The model achieved 91% sensitivity for detecting stage I cancers across 9 cancer types. Moreover, mitochondrial DNA (mtDNA) mutations and copy number changes in cfDNA have been associated with early colorectal cancer [17]. Overall, these studies demonstrate that cfDNA analysis, especially when combined with biophysical properties like fragment length profiles, methylation patterns, and mitochondrial genome alterations, provides a promising approach to detect cancers at early stages when treatment is most effective.

The analysis of circulating cfDNA offers several advantages over traditional tissue biopsies for cancer diagnosis and monitoring. Its non-invasive nature allows for easy, repeated sampling to track real-time changes in tumor genetics and treatment response [18]. In addition, the cfDNA analysis provides a comprehensive molecular portrait of cancer, capturing intra- and inter-tumor heterogeneity [3]. It can detect emerging mutations associated with drug resistance earlier than imaging techniques [19]. Other benefits include wider access and better patient compliance. However, cfDNA testing also has some limitations. Sensitivity can be a challenge in early-stage cancers shedding small amounts of ctDNA into circulation [20]. And, the specificity needs improvement to distinguish malignant mutations from age-related clonal hematopoiesis [21,22]. In addition, contamination with normal cell DNA can mask tumor-specific signals [3]. Furthermore, there is a lack of standardization in sample collection, processing protocols and mutation calling algorithms [3]. These factors can influence test accuracy. Variability in biological factors like tumor stage, location, vascularity, and mechanism of DNA release also affect ctDNA levels [23–28]. Overall, cfDNA analysis holds significant promise for non-invasive diagnosis and monitoring of cancers, but requires robust analytical and clinical validation before routine implementation.

Declarations

Conflicts of interest

The authors have no conflict of interests to disclose.

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