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DEVELOPMENT AND VALIDATION OF A NOVEL DIGITAL PCR ASSAY TARGETING CIRCULATING TUMOR DNA METHYLATION BIOMARKERS FOR HEPATOCELLULAR CARCINOMA SCREENING.

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Background : Hepatocellular carcinoma (HCC) is the most common type of liver cancer and the third leading cause of cancer-related deaths worldwide in 2020. However, current HCC screening tests, including serum alpha-fetoprotein (AFP) and ultrasound, are still limited by low accuracy. This study aims to discover and validate new HCC specific biomarkers in blood samples.

Methods : To select HCC-specific biomarkers, DNA methylation profiles of >10,000 tissue samples from HCC, normal, and other cancers were analyzed using a high throughput public database. A multi-step biomarker selection process using digital PCR identified the 3 HCC-associated CpG sites and validated these biomarkers in cancer cell lines, tissues, and plasma samples.

Results : All three biomarkers showed hypermethylation in liver cancer cell lines, indicating their high specificity for HCC. Two biomarkers were significantly hypermethylated in HCC, and the third showed liver tissue-specific methylation patterns. In addition, a novel digital PCR-based detection system using three biomarkers, termed the HEPA eDX, was optimized and subsequently validated in plasma samples including healthy individuals, patients with liver diseases, and HCC patients. This validation achieved a sensitivity of 80% (95% CI, 50.9-91.3) and a specificity of 96.7% (95% CI, 88.5-99.6), and the HEPA eDX showed superior performance for HCC detection compared to AFP.

Conclusions : The HEPA eDX test has demonstrated outstanding sensitivity and specificity, establishing its potential as a superior alternative to current HCC screening methods such as AFP.

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