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Exhaled breath and urinary volatile organic compounds (VOCs) for cancer diagnoses, and microbial-related VOC metabolic pathway analysis

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ADMINISTRATIVE INFORMATION

Support - This work was supported by the Natural Science Foundation of Qinghai Province (No. 2022-ZJ-912).

Review Stage at time of this submission - Data analysis.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 15 August 2023 and was last updated on 15 August 2023.

INTRODUCTION

Review question / Objective The objective of this present study was to conduct a comprehensive review and meta-analysis of prior research on volatile organic compounds (VOCs) found in exhaled breath and urine, with the purpose of detecting cancer. Additionally, our work aimed to investigate the metabolic pathways linked to the development of cancerous tumors, as VOCs are indicative of tumor and human metabolism.

Condition being studied Cancer poses a global public health concern and remains the leading cause of mortality worldwide. The identification of cancer at an early stage, coupled with effective treatment, has the potential to significantly enhance survival rates among patients. Given the prolonged asymptomatic period commonly associated with tumors, resulting in clinical diagnosis at an advanced disease stage, the imperative to develop novel methodologies centered on noninvasive and accurate biomarker detection becomes paramount. Such advancements hold the promise of facilitating timely identification and reducing mortality rates.

METHODS

Participant or population Different types of cancer patients.

Intervention This study is a diagnostic meta-analysis and there is no intervention group.

Comparator Healthy controls or non-cancer controls.

Study designs to be included Diagnostic research, whether prospective or retrospective.

Eligibility criteria The inclusion criteria for diagnostic studies were as follows: (1) utilization of either e-Nose technology or mass spectrometry; (2) cancer screening; and (3) examination of exhaled breath or urine. Conversely, studies were excluded if they met any of the following criteria: (1) not conducted on human subjects; (2) analysis of alternative biofluids such as blood or feces; and (3) inadequate provision of information required for diagnostic value calculations.

Information sources Two reviewers conducted a comprehensive literature search using the PubMed database to determine the overall diagnostic performance of VOCs in detecting tumors. The following search terms were used: (volatile organic compounds OR VOCs) AND (Neoplasms[Mesh] OR cancer OR carcinoma OR tumor OR neoplasm). The search included studies published up until June 30, 2023, without any lower date limit.

Main outcome(s) The pooled sensitivity, specificity and the area under the curve (AUC) for cancer screening utilizing exhaled breath and urine were determined to be 0.89, 0.88, and 0.95, respectively. A pretest probability of 51% can be considered as the threshold for diagnosing cancers with VOCs. As the estimated pretest probability of cancer exceeds 51%, it becomes more appropriate to emphasize the "ruling in" approach. Conversely, when the estimated pretest probability of cancer falls below 51%, it is more suitable to emphasize the "ruling out" approach. The heterogeneity observed in our study can be attributed to several factors, including nation, tumor type, sample size, source of VOCs, analytical platforms, and types of the control group, as revealed by meta-regression analysis and subgroup analysis. A total of 79, 102, 49, and 42 unique VOCs were identified in relation to lung, colorectal, breast, and liver cancers, respectively. Our investigation has revealed a notable enrichment of the metabolic pathway linked to microbial-related VOCs within the butanoate metabolism across these 4 types of tumors.

Data management The evaluation of study quality was conducted by two researchers who utilized the QUality Assessment of Diagnostic Accuracy Studies (QUADAS-2) checklist tool. Studies with a total score of 9 points or higher were selected, and any discrepancies were resolved through consensus.

Quality assessment / Risk of bias analysis The evaluation of study quality was conducted by two researchers who utilized the QUality Assessment of Diagnostic Accuracy Studies (QUADAS-2) checklist tool. Studies with a total score of 9 points or higher were selected, and any discrepancies were resolved through consensus.

Strategy of data synthesis Diagnostic parameters for VOCs were computed using the following formulas in each study: sensitivity = Tp divided by the sum of Tp+Fn, specificity = Tn divided by the sum of Tn+Fp, positive likelihood ratio (PLR) = sensitivity divided by one minus specificity (1-specificity), negative likelihood ratio (NLR) = one minus sensitivity (1-sensitivity) divided by specificity, and diagnostic odds ratio (DOR) = Tp multiplied by Tn divided by Fn multiplied by Fp. Additionally, their 95% confidence intervals (CI) were determined. The bivariate model was adjusted to calculate the area under the curve (AUC). Fagan's nomogram was designed to leverage the findings from our diagnostic analysis for the purpose of estimating the likelihood of cancer in patients. In order to identify the potential determinants of accuracy estimates, we endeavored to investigate the underlying causes of variability among the studies included in our analysis, specifically focusing on those with a quantified I2 value exceeding 50%. Given the significance of the threshold effect as a contributing factor to heterogeneity, we conducted an assessment using Spearman's correlation coefficient, whereby a negative correlation ($P<0.05$) would indicate the presence of said threshold effect. In the absence of a threshold effect but with the presence of significant heterogeneity, additional meta-regression analysis and subgroup analysis were conducted to investigate alternative factors contributing to heterogeneity in the studies included. Additionally, Deeks funnel plot symmetry test was employed to directly assess publication bias. The statistical analyses were performed using Stata 17.0 (StataCorp), with all tests being two-sided and a P value less than 0.05 considered as statistically significant.

Subgroup analysis In order to investigate the origins of heterogeneity, we conducted meta-regression and subgroup analysis across different dimensions, such as the nation of the included patients, tumor type, control group, sample size, test sample, and analytical platform.

Sensitivity analysis In order to identify the potential determinants of accuracy estimates, we endeavored to investigate the underlying causes of variability among the studies included in our analysis, specifically focusing on those with a quantified I2 value exceeding 50%. Given the significance of the threshold effect as a contributing factor to heterogeneity, we conducted

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Country(ies) involved China (Women's Hospital of Jiangnan University).

Keywords Cancer; Volatile organic compounds; Electronic nose; Diagnosis; Pathway analysis; Microbiota.

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