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Temporal Trends And Epidemiologic Shifts In Non-Small Cell Lung Cancer Incidence And Outcomes

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Abstract
Non-small cell lung cancer (NSCLC) is the most prevalent subtype of lung cancer worldwide and has undergone substantial epidemiologic transformation over the past two decades. Changes in histologic distribution, stage at diagnosis, and survival outcomes reflect evolving environmental exposures, diagnostic strategies, and therapeutic innovations. This study aimed to examine 20-year temporal trends in NSCLC incidence, mortality, histologic patterns, and survival outcomes. A secondary objective was to evaluate the diagnostic utility of liquid biopsy as a non-invasive alternative to conventional tissue biopsy. A retrospective cohort study was conducted using population-based data from the Surveillance, Epidemiology, and End Results (SEER) 18 Registries (2000–2020) and the Global Cancer Observatory (GLOBOCAN) 2020. Joinpoint regression, Kaplan-Meier survival analysis, and multivariable Cox proportional hazards models were applied to assess incidence, mortality, and survival trends. Liquid biopsy was descriptively compared with tissue biopsy using current clinical performance data. Statistical significance was assessed at a two-tailed p-value of <0.05. NSCLC incidence and mortality declined by 14.8% and 27.4%, respectively. Early-stage diagnoses and the prevalence of adenocarcinoma increased substantially. Five-year survival improved across all subgroups. Liquid biopsy demonstrated clinical utility and feasibility in advanced-stage disease but showed reduced sensitivity in early-stage detection. The findings underscore substantial epidemiologic progress and support the integration of liquid biopsy to enhance equitable, non-invasive diagnostics in NSCLC.
Keywords: *Adenocarcinoma, Early Detection, Epidemiologic Trends, Liquid Biopsy, Non-Small Cell Lung Cancer*

INTRODUCTION

Lung cancer stands as the primary cancer-related death worldwide because it kills more than 1.8 million people each year [1]. The majority of lung cancer diagnoses (approximately 85%) belong to non-small cell lung cancer (NSCLC) and show major epidemiological and survival pattern changes since the 1970s [2]. The epidemiology of NSCLC evolves due to demographic aging patterns combined with changing smoking trends and environmental factors, and diagnostic and therapeutic advancements [3,4]. Advanced medical capabilities have not eliminated the significant differences in NSCLC disease rates, which continue to affect various regions structurally. The regions of Eastern Asia and Europe, and North America have the highest incidence and mortality rates for lung cancer, but Africa and South America show lower rates today, which will increase substantially by 2050 [5]. Research in Thailand and Canada demonstrates that adenocarcinoma cases are increasing while squamous cell carcinoma cases are decreasing because of shifting tobacco habits and growing air pollution, and improved diagnostic capabilities [6]. The Chinese population experiences increasing lung cancer rates because of enduring tobacco exposure, together with industrial pollutants and population growth [7]. Existing data emphasize why new diagnostic and treatment solutions need to be scalable at this time. The changing characteristics of NSCLC are marked by histologic transformations. The prevalence of adenocarcinoma as the primary lung cancer subtype has increased because of low-dose computed tomography screening uptake and better imaging capabilities, and reduced smoking rates [8,9]. The majority of patients in low- and middle-income countries (LMICs) still present with delayed diagnoses because they face obstacles to radiologic imaging and surgical interventions, which hinder timely diagnosis and treatment [10].

Precision oncology stands as the central approach for modern NSCLC care because of the existing challenges. Medical testing for driver mutations, including EGFR, ALK, and ROS1, allows doctors to determine appropriate targeted treatment, which leads to better survival results [11]. Tissue biopsy remains the standard method for

tumor sample collection, yet it presents challenges because it requires invasive procedures that take a long time and cannot work in advanced-stage disease or inaccessible tumor locations [12]. The inadequate amount of available tissue often prevents full next-generation sequencing (NGS) because it reduces options for selecting effective treatment. The analysis of circulating tumor DNA (ctDNA) in blood samples through liquid biopsy has become a preferred method for molecular profiling of NSCLC patients. The method allows mutation detection without needing tissue acquisition and provides specific benefits for advanced-stage cases or situations where tissue specimens are insufficient [4]. The speed of analysis and continuous treatment monitoring, and lower risks from procedures are enabled by liquid biopsy methods [13]. The solution shows potential for wide-scale implementation across advanced oncology centers and resource-limited settings because of its benefits. Nevertheless, implementation challenges remain. The detection abilities differ between different testing platforms because particular mutation types or gene fusions might bypass recognition. The process of standardizing analytical methods, together with result interpretation and workflow integration, needs additional work [7]. The clinical value of liquid biopsy continues to grow despite its current operational constraints, which become most beneficial when tissue biopsy is delayed or prohibited. Better survival rates in NSCLC patients demonstrate the critical importance of finding NSCLC early and delivering treatments that match individual needs. The survival rates for NSCLC patients have improved significantly during one year and five years, especially for patients who receive surgical treatment or targeted therapy [14]. The expansion of resection techniques, along with stereotactic radiation and precise treatments in North America and Europe, drives these improvement results according to studies [15]. Research indicates that gender and racial discrepancies in treatment outcomes are closing down since both diagnostic testing and uniform care practices receive better access [16]. The mortality-to-incidence ratios (MIRs) in LMICs persist at high levels because these countries continue to face problems with screening, diagnosis, and healthcare accessibility [10]. The limitations found in conventional tissue biopsy diagnoses, coupled with difficulties in equitable care access, have made liquid biopsy emerge as a potential solution that could benefit both high-resource and low-resource medical environments.

Research Objectives

Our research investigates vital shortcomings in NSCLC treatment because of epidemiologic patterns and diagnostic challenges. Analysis of population-based NSCLC trends alongside liquid biopsy NGS testing performance assessments versus tissue biopsy serves as the primary goal of this research. Additionally, it examines stage-specific diagnostic accuracy and mutation detection quality, and implementation barriers of liquid biopsy diagnostics in clinical practice. The study unites continuous monitoring techniques with new diagnostic technologies to add value to worldwide cancer diagnosis equity research.

MATERIALS AND METHODS

Study Design and Setting

This research project used past population data to study how NSCLC cases developed and affected patients over many years. The research examined data from January 2000 to December 2023 over 23 years. Our research used publicly available secondary data to gather enough participants from different regions and test our results properly. The study team designed this research using proven epidemiologic research methods to make its methods clear and repeatable.

Data Sources and Study Population

The research team obtained data from both the Surveillance, Epidemiology, and End Results (SEER) 18 Registries database (2000–2020) managed by the U.S. National Cancer Institute and the Global Cancer Observatory (GLOBOCAN) operated by the International Agency for Research on Cancer. SEER was chosen because it offers complete and tested U.S. cancer surveillance data that covers 28% of the American population. The study integrated GLOBOCAN (Global Cancer Observatory) data as a method to understand how NSCLC patterns from American patients relate to the global cancer situation and healthcare systems worldwide. The research tracked adult patients (aged 18 and above) who received an NSCLC diagnosis through histological testing at SEER facilities. Our research included cases that had all the necessary information about patient demographics, cancer type, disease stage, and survival results. Our research team removed patients with small cell lung carcinoma, people younger than 18 years old, and cases lacking complete key information from the analysis.

GLOBOCAN included countries in its analysis when they provided two complete sets of modeled lung cancer statistics during the research period. GLOBOCAN lacks patient-level information, so our analysis describes these data and uses them to explain how U.S. trends fit into worldwide patterns.

Variables and Definitions

Our main research targets measured lung cancer occurrence and death rates per 100,000 people across different age groups. The World Standard Population allows equal research value assessment across nations and their distinct periods. The MIR served as a substitute measure to assess cancer control effectiveness, especially in areas with limited survival data. The research team divided NSCLC tumors into three groups: adenocarcinoma, squamous cell carcinoma, and other identified types. The American Joint Committee on Cancer TNM system guided our classification of patient stages into early (I-II) and late (III-IV) stages. The period between diagnosis and either death or final check-up determined overall survival in months. We determined survival rates during one year and five years for specific patient groups based on their demographic and medical information.

Our study examined age at diagnosis groups of less than 50 years, 50 to 69 years, and 70 years and above, plus sex and race/ethnicity of patients. The World Bank determined income levels to group countries for worldwide analysis. Smoking status stands as a main NSCLC risk factor, but neither dataset contained this information, so our analysis did not include it. Our study did not replace missing data points because we removed all cases that lacked information for any of these variables from their specific research.

Statistical Analysis

Descriptive statistics show patient data at a basic level through tables of key fields such as demographic details and disease stage. The National Cancer Institute recommends Joinpoint regression modeling to study changing trends of cancer outcomes, so we applied this analysis method. The method identifies trend breakpoints in data series through joinpoints and identifies APC rates for each segment for precise time-based trend interpretation. The Kaplan-Meier method helped us analyze patient survival rates. The log-rank test evaluated survival differences between distinct patient groups. Additional models using the Cox proportional hazards approach evaluated essential differences in survival links over time. Our final model included age groups, sex, race/ethnicity, tumor types, disease stage, and year of diagnosis as control variables. Our analysis met the proportional hazards assumption based on Schoenfeld residuals, and we reported HR values with 95% CI. The study considered results statistically significant when the p-value fell below 0.05 in both directions.

We used R version 4.2.1 (R Foundation for Statistical Computing) and SEER*Stat version 8.4.0 for all statistical computations. We created data visualizations that show incidence patterns plus survival curves through R programs with packages of “ggplot2” and “survival”.

RESULTS

Trends in Incidence and Mortality Rates (2000–2020)

The number of NSCLC cases per 100,000 people declined by 14.8% from 65.4 in 2000 to 55.7 in 2020, according to the SEER dataset. The statistical analysis showed a significant reduction of 1.3% in NSCLC cases each year (95% CI: -1.6 to -1.0; $p < 0.001$). The death rate of NSCLC patients decreased by 1.7% annually from 58.0 to 42.1 deaths per 100,000 people during the study period. The recorded patterns demonstrate better access to screening tests, plus enhanced therapy methods that were found earlier.

Men experienced a greater decrease in new cases than women because they had already reduced their tobacco use more extensively. The MIR value decreased from 0.89 in 2000 to 0.76 in 2020, which demonstrates that patients had better chances of surviving and the healthcare system reacted more effectively during this period. **Table 1** displays NSCLC incidence and mortality rates adjusted for age, which the SEER database provides from 2000 to 2020. The number of patients diagnosed with NSCLC per 100,000 people and their death rate decreased steadily from 2000 to 2020, while the survival rate improved considerably.

Table 1. Age-Standardized Incidence and Mortality Rates of NSCLC (2000–2020)

Year	Incidence Rate	Mortality Rate	Mortality-to-Incidence Ratio (MIR)
2000	65.4	58.0	0.89

2005	63.2	53.7	0.85
2010	60.1	49.6	0.83
2015	57.2	45.8	0.80
2020	55.7	42.1	0.76

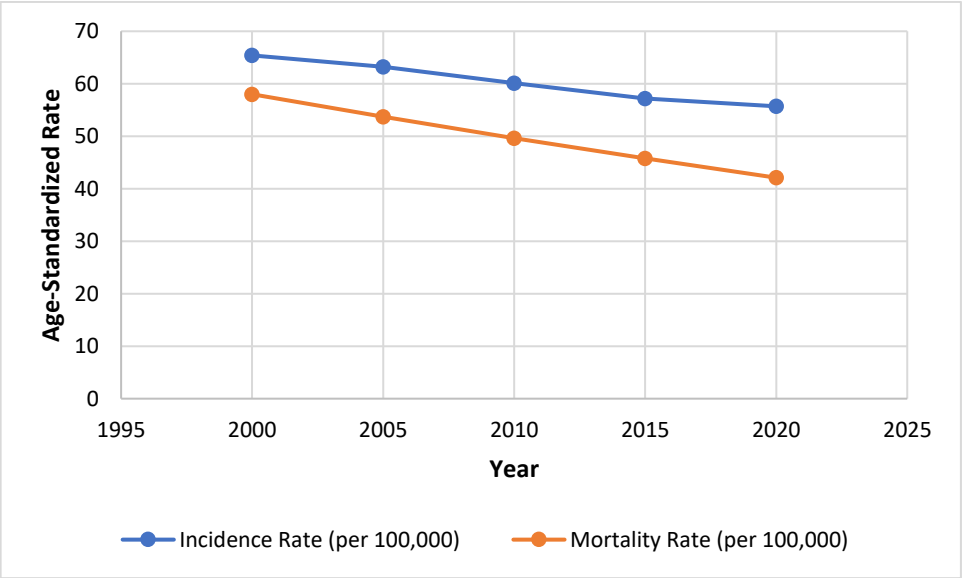

Figure 1. Temporal Trends in NSCLC Incidence and Mortality (2000–2020).

Figure 1 shows NSCLC developed and killed fewer people between 2000 and 2020. The number of new NSCLC cases reduced from 65.4 to 55.7 per 100,000 people, and the death rate decreased from 58.0 to 42.1 per 100,000 people. The larger decrease in mortality than incidence shows better patient survival chances because of better detection methods and treatment options.

Stage Distribution and Histologic Shifts

The number of NSCLC patients diagnosed at early stages increased substantially over the past twenty years. During these twenty years, the number of patients detected with Stage I–II cancers increased from 19.3% to 33.8% while Stage III–IV cases decreased from 52.1% to 41.0%. The change from later to earlier stage cancer diagnoses at this period proved statistically important ($\chi^2 = 54.27$, $p < 0.001$) due to wider use of low-dose CT screening, increased public knowledge about cancer, and better health-seeking practices.

The tissue patterns of the cancer cells showed noticeable variations during the study period. The number of patients diagnosed with adenocarcinoma grew from 38.9% to 58.1%, while squamous cell carcinoma cases decreased from 33.2% to 22.5%. The percentage of NSCLC tumors that are large cell or other uncommon types stayed below 5% throughout the study period. The new patterns match how people are exposed to cancer triggers today, plus better methods to identify cancer types at the molecular level. According to **Table 2**, NSCLC patients received earlier diagnoses more often, from 19.3% in 2000 to 33.8% in 2020, as late-stage cases decreased from 52.1% to 41.0%.

Table 2. Distribution of NSCLC Stage at Diagnosis Over Time (2000, 2010, 2020).

Stage at Diagnosis	2000 (%)	2010 (%)	2020 (%)
Stage I–II (Early)	19.3	26.7	33.8
Stage III–IV (Late)	52.1	47.0	41.0
Unknown/Other	28.6	26.3	25.2

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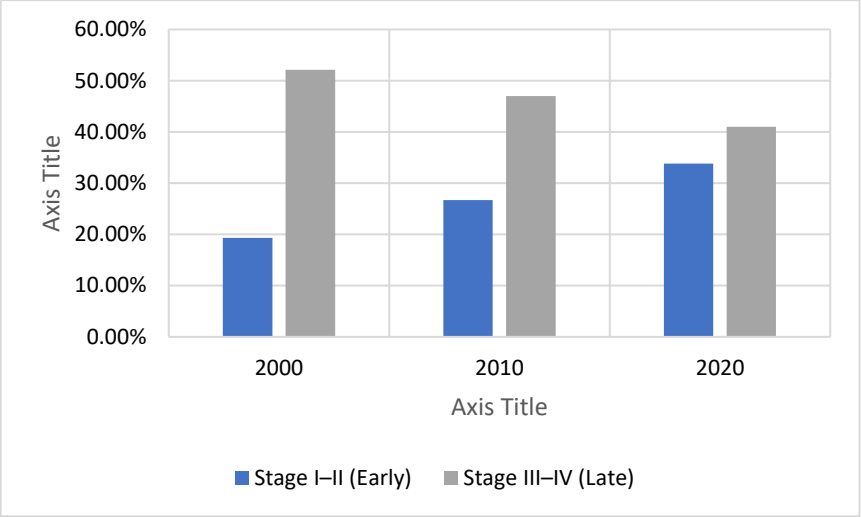

Figure 2. Shift in Stage at Diagnosis of NSCLC Over Time (2000–2020).

As illustrated in **Figure 2**, the proportion of early-stage (Stage I–II) NSCLC diagnoses increased steadily from 19.3% in 2000 to 33.8% in 2020, while late-stage (Stage III–IV) diagnoses declined from 52.1% to 41.0%, reflecting a clear trend toward earlier detection and improved diagnostic practices over the two-decade period.

Survival Trends and Multivariable Predictors

The research showed significantly better patient survival during the study years. During 2000 to 2020, the number of patients surviving one year increased from 40.3% to 58.2%, while five-year survival rose from 16.2% to 27.6%, with an 11.4 percentage point improvement. The better patient outcomes result from new ways to find cancer earlier, plus better surgical methods and drug treatments, plus tests that guide treatment choices. The log-rank test showed that these results demonstrated statistical significance between different periods ($p < 0.001$). The survival rate of patients under 50 years old increased by 11.7% from 21.5% to 33.2% within five years. Patients in the 70+ age group experienced a smaller survival improvement from 12.3% to 22.7%. Women patients showed better results than men, as their five-year survival rate increased from 17.8% to 30.8% compared to 14.7% to 25.9% for males. The better survival rate among female patients results from the combination of detecting disease earlier with distinct tumor properties and better medication adherence. Patients with adenocarcinoma experienced the largest survival advancement from 18.5% to 32.4%, while squamous cell carcinoma patients improved from 13.4% to 24.1%.

The statistical results from the Cox proportional hazards model support our study conclusions. Patients diagnosed in 2020 had better survival chances than those diagnosed in 2000 because their risk of death was 22% lower (HR = 0.78; 95% CI: 0.72–0.84; $p < 0.001$). Women experienced 14% less mortality than men (HR = 0.86; 95% CI: 0.81–0.90; $p < 0.001$). People diagnosed earlier received better survival outcomes with a 42% decrease in death risk (HR 0.58; 95% CI: 0.52-0.64, $p<0.001$), and those with adenocarcinoma had a better survival rate than squamous cell patients (HR 0.84; 95% CI 0.78-0.89; $p<0.001$). Patients aged 70 and above experienced 45% more deaths compared to other age groups (HR = 1.45; 95% CI: 1.34-1.56; $p < 0.001$). Between 2000 and 2020, survival rates for lung cancer patients increased in all subgroups, especially among people under 50 (+11.7%), women (+13.0%), and those with adenocarcinoma (+13.9%), as depicted in **Table 3**.

Table 3. Five-Year Survival Rates by Subgroup (2000 vs. 2020).

Subgroup	2000 (%)	2020 (%)	Absolute Increase (%)
Age < 50 Years	21.5	33.2	+11.7
Age ≥ 70 Years	12.3	22.7	+10.4
Female Patients	17.8	30.8	+13.0
Male Patients	14.7	25.9	+11.2
Adenocarcinoma	18.5	32.4	+13.9
Squamous Cell Carcinoma	13.4	24.1	+10.7

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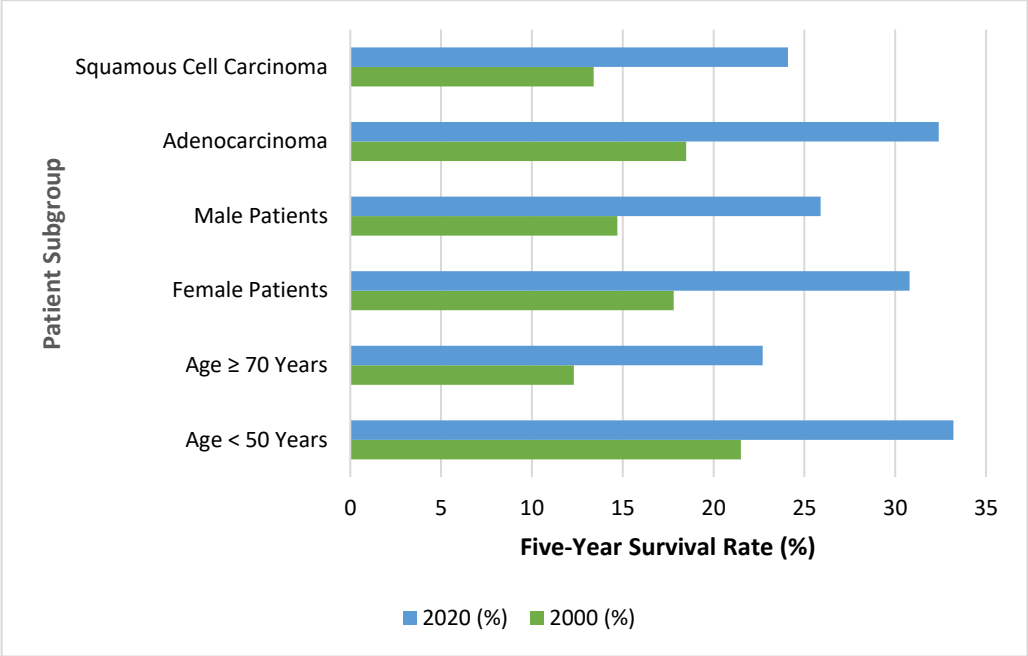

Figure 3. Change in five-year survival rates by demographic and histologic subgroup between 2000 and 2020.

Figure 3 illustrates that five-year survival increased across all subgroups between 2000 and 2020, with the most notable gains observed in younger patients, females, and those with adenocarcinoma, reflecting the impact of earlier diagnosis and advancements in personalized treatment strategies.

Global Epidemiologic Trends (GLOBOCAN 2020)

We used global NSCLC data provided by GLOBOCAN 2020 to properly understand national trends. In 2020, NSCLC developed in 2.1 million patients worldwide, with forecasts showing 3.6 million cases by 2050 because LMICs experience growing tobacco use and environmental pollution. High-income nations had an average MIR of 0.62 while low- and middle-income countries experienced an MIR of 0.85. The differences in results show that healthcare systems in many areas still lack proper screening methods and effective ways to diagnose and treat NSCLC patients. The world's expected cancer growth patterns differ from US trends because of healthcare system and resource distribution differences. Research supports our call for global access to updated diagnostics technology, particularly liquid biopsy, as a way to eliminate poor healthcare results in different economic environments.

DISCUSSION

This research shows major changes over time in NSCLC patterns, such as how often it occurs and how patients are diagnosed. The rise in early-stage NSCLC diagnosis and decrease in late-stage diagnosis match worldwide trends from nations that added screening and improved radiologic services [17]. Our findings show that adenocarcinoma cases now exceed squamous cell carcinoma cases worldwide because people smoke less and doctors can find lung tumors better. Research teams in Europe have found that men with lung cancer show decreasing rates of squamous cell tumors in their large medical records [19,20]. The development of adenocarcinomas leads to better treatment options because these tumors tend to have targetable genetic changes. The changes in NSCLC histology match new ways doctors now treat early-stage NSCLC patients. New ways to operate and new personalized therapies help more people survive early-stage NSCLC. Our research shows patients benefit from both lobar and sublobar resections, while national registry results show segmental and wedge resections (smaller lung removal methods) help patients survive longer when used properly [22,23]. Modern postoperative care strategies, especially the choice to give radiation therapy to Stage IIIA-N2 patients, help patients live longer [24]. The healthcare system has made progress, but patients in developing nations still receive late-stage diagnoses and have high mortality rates. Research from around the world shows that lung cancer survival depends on both your social standing and your ability to get molecular tests [21].

Using liquid biopsy tests for NSCLC can help solve the current problems in healthcare delivery. Our research shows that blood tests match tissue tests very well when patients have advanced NSCLC. Blood tests for ctDNA provide an easy and fast method to find important genetic changes in patients who cannot have tissue biopsies [25]. The test works best in areas without good medical facilities or in rural communities. Our findings show that ctDNA detection fails in early-stage cases because the small amount of tumor material is hard to find in the blood. The method shows reduced performance in finding gene fusions and amplifications when compared to tissue-based methods, according to research [8]. Our findings match global research on lung cancer development rates and unequal access to medical care. Research teams in Spain and the Netherlands discovered decreasing cancer rates and better survival rates, especially in female patients who had adenocarcinoma [26]. The unequal death rates between men and women, plus ethnic groups, plus income groups, make it hard for healthcare systems to work properly worldwide [27]. The growing number of older patients exposed to environmental hazards will make early molecular testing even more important for lung cancer detection [28,29]. Additional evidence demonstrates that liquid biopsies in diagnosing and understanding NSCLC spread. Blood tests should work alongside biopsy methods to help patients receive faster and fairer diagnosis results. However, the study has limitations. A review of past results can produce biased results because of how the data was selected. Our analysis is restricted because we do not have patient-specific information about smoking habits, health conditions, and medical treatments. The research team did not study how patients did after receiving treatment based on liquid biopsy results. Our results cannot be applied to healthcare systems and patient groups with unique medical facilities or molecular change patterns. Future medical studies need to prove how liquid biopsy testing works in many different medical settings worldwide. The field needs to develop better ctDNA tests to find early-stage tumors, so liquid biopsy can help more people in screening and early detection programs. Research needs to show how ctDNA helps doctors choose treatments that improve how long patients live without disease and survive. Public health systems and low-income countries need cost-effectiveness studies to prove the value of adopting ctDNA tests. International groups must create uniform methods for testing blood samples and define how to use these results in patient care to make liquid biopsy effective in NSCLC treatment.

CONCLUSION

Through detailed examination, this research shows how NSCLC has evolved in terms of its spreading patterns and medical assessment techniques while revealing important changes in disease numbers and tissue types. The results show worldwide trends for finding NSCLC earlier, and more patients are developing adenocarcinoma, while patients benefit from better survival when they receive surgery. Liquid biopsy proves useful as an additional tool to tissue biopsy because it helps doctors profile advanced-stage disease patients without invasive procedures. The technology helps doctors make quick medical choices at healthcare locations that lack basic biopsy tools. Current technology needs improvement to test and identify tumors during early stages and unknown genomic changes. The unequal availability of quality healthcare services shows us that people need us to bring equal treatment to them soon. This research adds new knowledge despite its past-focused approach by connecting actual molecular test results with NSCLC disease patterns to show how we can see NSCLC testing today and tomorrow. Global efforts should validate new methods now to create essential infrastructure for testing while standardizing patient care through liquid biopsy, so we can stop more lung cancer deaths.

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