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NARRATIVE REVIEW

Lung Cancer in Never Smoking Asian Populations

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Introduction: Lung cancer incidence is disproportionately higher in Asian individuals who have never smoked compared with non-Asian counterparts. While epidemiologic determinants remain unclear, risk factors appear to include environmental exposures, oncogenic drivers, and sex-specific patterns. Understanding these factors may lead to effective screening and treatment. This narrative review synthesizes the current state of research on lung cancer in never-smoking Asian populations, comparing disease characteristics between persons from Asia and the Asian diaspora.

Methods: Literature related to lung cancer in never smoking-Asian populations living in and out of Asia and published during January 1, 2018–August 17, 2024, were included. PubMed was searched for observational studies, interventional studies, and existing systematic reviews for articles published in English. Independent reviewers screened and conducted full text review and then synthesized insights from the articles by consensus.

Results: Studies published during 2018–2024 indicated that lung cancer among Asians who have never smoked is influenced by genetic, environmental, and lifestyle factors, with a higher incidence of adenocarcinoma and younger age of diagnosis among Asian and Asian American women. Increased lung cancer incidence was observed among populations who have never smoked, especially within Asian populations. Targeted therapies, in addition to standard surgical resection, have improved survival in patients with epidermal growth factor receptor, anaplastic lymphoma kinase-positive, and other actionable mutations, which are common in this population. However, treatment resistance and limited benefit from immunotherapy constrain long-term outcomes. Future strategies, such as novel targeted agents, combination regimens, and biomarker-driven monitoring, were found to extend progression-free survival and personalize care.

Conclusions: Lung cancer among Asian populations who have never smoked represents a biologically distinct, often targetable disease entity that necessitates rethinking of screening eligibility and treatment paradigms. Limitations of smoking-based risk models, emerging resistance to therapies, and geographic disparities in diagnostic and treatment access, both within Asian and across communities of the Asian diaspora, highlight the urgent need for more inclusive screening criteria, improved resistance management strategies, and equity in precision oncology deployment across Asian subpopulations. Improvements for screening programs should aim to maximize accurate detection while minimizing overdiagnosis.

Key Words: Never-smoker ▪ lung cancer ▪ lung neoplasms ▪ small cell lung carcinoma ▪ non-small cell lung carcinoma ▪ adenocarcinoma of lung ▪ early detection ▪ screening ▪ epidemiology ▪ treatment ▪ Asian ▪ Asian American

Lung cancer remains the leading cause of cancer-related deaths in the United States and worldwide.[1] While tobacco smoking is the primary risk factor, accounting for 76.2% of lung cancer deaths in 2019,[2] smoking rates worldwide have been declining, projected by the World Health Organization (WHO) to decrease from 33% of adults in 2000 to 18% by 2030. The United States has seen a clear correlation between this decline and a decrease in lung cancer incidence.[3] However, lung cancer incidence is expected to increase through 2035 in most European, Eastern Asian, and Oceanian countries mainly due to population aging and growth.[1,2] As lung cancer incidence continues to increase, a growing proportion of cases will involve individuals who have never smoked.[4,5] This change underscores the urgent need to deepen our understanding of the etiology of lung cancer in people who have never smoked (LCINS).

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Observing the data further, many studies have shown that, among lung cancer patients, a higher proportion of cases among Asian persons occur in those who have never smoked compared with the proportion seen among non-Asian populations.[6–9] This elevated proportion of LCINS cases in Asian populations guides the aim of this study. While prior reviews have examined LCINS broadly[10] or focused on East Asian populations living in Asia[11], none have integrated epidemiology, risk factors, screening performance, and treatment patterns across both Asian populations in Asia and Asian diaspora communities. This integration is essential because LCINS incidence and molecular profiles vary substantially across settings, and a clearer understanding of how ancestry, environment, and health-system context interact aids in the development of accurate risk prediction models, optimization of screening strategies, and ultimately the improvement of clinical outcomes.

In this review, population group terminology follows previously published definitions,[11] the MeSH system, and the United Nations geoscheme, which groups countries into continental regions. The term "Asian" was used broadly to refer to individuals originating from the continent of Asia. "East Asian" referred to populations from China (including Hong Kong), Japan, Mongolia, Taiwan, North Korea, and South Korea. "South Asian" pertains to populations from the Indian subcontinent, including India, Pakistan, and Bangladesh.[11,12] These definitions were used for consistency in discussing epidemiologic patterns in LCINS. As the MeSH term for "Asian" did not include Taiwan or Hong Kong or Singapore,[13] these terms were included separately in the search strategy.

This review synthesized these domains to clarify how ancestry, environment, and health-system context differentially shape LCINS risk and outcomes. This structure reflects the central argument that LCINS in Asian populations represents a distinct, heterogenous disease entity that requires ancestry-informed risk assessment, tailored screening criteria, and population specific diagnostic and therapeutic strategies. To provide this overview, the epidemiology of LCINS, efficacy of screening, and current and emerging therapeutic landscape were reviewed. Therefore, this review included a global perspective to include data on LCINS among Asian individuals residing in diverse geographic contexts (e.g., United States, Australia, and New Zealand) to assess the contributions of environmental factors and genetic inheritance to disease patterns.

METHODS

To allow for a broad overview of LCINS among Asian populations, the types of articles included in this narrative review were observational studies, interventional studies, and existing systematic reviews. PubMed was searched for articles related to LCINS among Asian populations that were published during January 1, 2018–August 17, 2024. The search strategy included search terms of never smokers, lung cancer, LCINS, and Asian populations (Supplemental Table 1). Specific terms for Taiwan, Singapore, and Hong Kong were added in the search strategy to those of MeSH terms for Asian countries, which were limited to "Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam" in "Asian," but did not include Taiwan, Singapore, or Hong Kong.[13] Of note, genome-wide association studies (GWAS) and polygenic risk score studies (PRS) were not included in the narrative review because a previous study had covered GWAS and PRS studies among Asian populations.[11]

The search strategy returned 119 journal articles. To organize title and abstract screening, the web-based collaboration software platform Covidence was used. Two independent reviewers (LL and RL) conducted title and abstract screening, 43 articles were excluded and 76 articles remained. A large proportion of excluded articles were GWAS or related molecular studies (15/43), PRS or related prediction studies (9/43), or not relevant to LCINS (10/43). The other excluded articles did not focus on Asian populations (6/43), were not in English language (1/43), was a case report (1/43), or was a database profile (1/43).

Full text review and synthesis of insights from the remaining 76 articles were conducted by two pairs of two independent reviewers (JK, SG, AK, EC). Because the goal was to contextualize LCINS within clinical, epidemiologic, and implementation frameworks relevant to Asian populations, studies with direct implications for screening, diagnosis, and treatment were prioritized. There were no discordances about inclusion during full text review, and each pair of reviewers worked and discussed together how to synthesize insights from the articles. During full text review, one additional article was included in this narrative review because it was cited by multiple other full text review articles. A second additional article was included to address a gap in discussion about future directions regarding screening, thus yielding a total of 78 articles.

RESULTS

Epidemiology

By focusing this narrative review on lung cancer among Asian who have never smoked, exploring contributing factors was imperative since smoking history was not a consideration. These factors included genetic predispositions, environmental exposures, and lifestyle choices that potentially play a significant role in the etiology of this disease. Environmental factors such as air pollution have long been discussed as an etiological explanation, but the existence of these trends amongst the Asian diaspora, or Asian populations outside of Asia, suggests other variables may be at play. Therefore, the contributions of factors ranging from sex differences to dietary consumption, in lung cancer incidence amongst Asians who have never smoked were explored (Table 1).

Ancestry

As evidenced in the literature, a higher proportion of lung cancer cases are made up of individuals from Asian populations from around the world who have never smoked.[6–8,14–16] When examining lung cancer trends in Asian populations, it is important to consider differences that may exist within two distinct groups: Asians living in Asia and the Asian diaspora. By analyzing trends shared or not shared within these groups, factors related to environmental exposure (living in Asia) or to genetic predispositions (similarities across Asians globally) can be distinguished.

Asians living in Asia

A study conducted in Taiwan found approximately 47% of newly diagnosed lung cancers are amongst people who have never smoked.[14] This number increased to 80.1% when stratifying the data to Asian women.[14] A study in Singapore indicated that 71% of lung cancer cases occurred in women who have never smoked.[15] A study conducted in Taiwan looking at the Taiwan Cancer Registry data during 1996–2018 found an increase in the proportion of LCINS cases from 49.9% in 2011 to 60.2% in 2018.[16] Complementing these findings, longitudinal data from Singapore demonstrated a rising proportion of never-smokers among newly diagnosed non-small cell lung cancer (NSCLC) cases, increasing from 31 to 48% over a decade.[17] This markedly higher proportion of LCINS cases amongst lung cancer cases in Asians living in Asia suggests potential environmental etiologies underlying these trends.

The Asian diaspora

Two studies conducted in Australia indicated that among those who never smoked, individuals born in Asian countries were at threefold higher risk of developing lung cancer compared with those born elsewhere.[7] Notably, Asian country of birth was the only factor significantly associated with LCINS cases, with no associations found in other pertinent factors such as passive smoking and family history of lung cancer.[7] Due to the lack of information regarding how long Asian-born Australians resided in Asia, it is difficult to discern whether this association is a result of genetic and/or environmental factors.

A study conducted in the United States, more specifically Northern California and Hawaii, indicated that among Asian American (AA) or Native Hawaiian or Other Pacific Islander (NHOPI) women diagnosed with lung cancer, 43.9% had never smoked.[6] Apart from Japanese American women, all AA and NHPI female ethnic groups had significantly elevated risks of lung cancer.[6] A study conducted in the U.S. state of Florida found that proportions of LCINS were highest among Asian and Pacific Islander men and women being 27.3% and 59.6%, respectively.[8] Together, these studies of Asian diaspora populations indicate that elevated LCINS risk persists even outside high-pollution Asian environments and suggested an inherited or ancestry-

Table 1. Overview of Epidemiology of LCINS among Asian Populations

Factors	Main findings
Ancestry	Elevated LCINS risk persists among Asian diaspora, suggesting ancestry-related components beyond environmental exposures in countries of origin.
Age and sex differences	Younger ages at diagnosis (e.g., Asian women diagnosed ~11 years younger than men; higher incidence in women aged 30–54); Women comprise >70% of LCINS cases.
Lung cancer type	Adenocarcinoma predominates (64–82% of cases); ground-glass nodules are more common in never-smokers.
Mutations	EGFR driver mutations are most frequent among Asians.
Cancer stage at diagnosis	LCINS often diagnosed earlier (40–71% early-stage), but women have 38% higher late-stage incidence.
Air pollution	PM2.5 exposure, indoor cooking fumes, and coal/biomass burning linked with increased LCINS risk.
Medical comorbidities	Impaired lung function, asthma, and tuberculosis are associated with elevated LCINS risk.
Telomere length	Longer leukocyte telomeres are linked with increased LCINS risk.
Family history	2–3x higher odds of LCINS with family history.
Dietary fiber and yogurt	High dietary fiber/yogurt intake linked with LCINS risk, though findings may be limited to squamous cell carcinoma.
Body mass index	Higher BMI associated with reduced risk in some studies, but no significant association observed in Asian-specific analyses; evidence remains inconclusive.

Abbreviations: BMI = body mass index, LCINS = lung cancer in non-smokers, EGFR = epidermal growth factor receptor, PM2.5 = particular matter less than or equal to 2.5 micrometers.

related component. This separation of environment versus genetic risk factors is central to understanding LCINS in Asian populations and might indicate the need for ancestry-informed screening models.

Age and sex differences

Chinese women who never smoked were diagnosed younger than their male counterparts with one cohort study reporting women being diagnosed an average of 11.3 years younger.[18] Notably, these trends were seen both in Asian populations residing in China and the United States, reinforcing the notion of a potential role of ethnicity rather than environment.[18] Another study from Taiwan found that, when comparing men and women of the same age group and the same cancer stage, women consistently had higher rates of lung adenocarcinoma, both those who had smoked and those who have never smoked.[19] This finding was consistent across a study conducted in the U.S. state of Florida, which indicated that LCINS cases were more common among women aged 30–54. While detailed sex-race stratification was not provided in this study, the particularly high absolute LCINS incidence among Asian women noted in the study being the highest of any race-sex group, suggested a likely contribution of age to this trend.[8]

The finding from various studies that Asian women who have never smoked are diagnosed with lung cancer at younger ages compared with Asian men who have never smoked is also concerning and necessitates further discussion pertaining to differences in LCINS attributable to sex. Of Asian LCINS cases, women make up the majority, at times over 70% of Asian LCINS cases.[6,9,18,19] To explain sex differences in LCINS cases, reproductive factors such as parity and oral contraceptive use have been investigated; however, results remain unclear. In one study performed in China, women who never smoked were found to have a 13% increased risk of lung cancer death for each additional live birth, a 2% increased risk of lung cancer death for each year since menopause, and a 22% increased risk of lung cancer death for oral contraceptive users.[20] Another study assessing cohorts from Japan, Korea, China, and Singapore evidenced a protective association of parity and lung cancer incidence in Asian women who never smoked, with parous women having a 18% decreased risk of lung cancer incidence compared with nulliparous women.[21] The authors suggested that this protective effect may have been due to the endogenous estrogen being involved in the EGFR and/or estrogen receptor pathways that mediate lung cancer risk. These findings underscore the need for more research to elucidate whether reproductive factors are protective or causative which might provide important information in assessing lung cancer risk amongst Asian women. Regarding ethnicity and sex differences in incidence, a U.S. study found that being of Asian descent and female sex were both associated with improved survival in lung cancer after controlling for relevant clinical and social factors.[22]

Types of lung cancer

Adenocarcinoma

Among Asian persons who have never smoked, the most common histological type of lung cancer is adenocarcinoma.[6–9,16,18,19,23–29] Adenocarcinoma is more common in those who have never smoked compared with those who have smoked. One U.S. study indicated adenocarcinoma accounted for 64.5% of lung cancer among females who never smoked compared with 46.5% among those who ever smoked.[6] These findings are consistent globally, as a study in Taiwan found similar results, with adenocarcinoma making up 82.3% of lung cancer among those who never smoked compared with 52.2% of LC among those who ever smoked.[23]

Ground-grass nodules and part-solid tumors

Lung cancer in individuals with a smoking history has strongly been associated with the presence of a solid tumor component.[10] This was corroborated by the results from the Taiwan Lung Cancer Screening in Never-Smoker Trial (TALENT) study, which found that the greatest proportion of lung cancer nodules occurred in populations that never smoked were ground-glass (48.0%) compared with part-solid nodules (32.9%) and solid nodules (19.1%).[30]

Mutations

The etiology of adenocarcinoma in individuals who never smoked typically has a genetic component, with the most frequent mutation being an EGFR driver mutation.[18,31] Asian persons were found to be 3.35 times more likely to have EGFR mutation-positive NSCLC compared with New Zealand Europeans.[31] The frequency of specific genetic mutations in addition to EGFR (i.e., mesenchymal-epithelial transition factor [MET], neuregulin receptor 1 [NGR1], c-ros oncogene 1 [ROS1], anaplastic lymphoma kinase [ALK], and kirsten rat sarcoma viral oncogene homologue [KRAS]) opens avenues for current and future treatment of Asian LCINS.

Stage at diagnosis

Cases of LCINS tend to be diagnosed at an earlier stage when compared with lung cancer in those who have smoked. A study conducted in Taiwan found

40.2% of LCINS cases were stages I or II compared with 25.6% in those who smoked.[23] Another study in Taiwan found 71.2% of LCINS cases were early stage (0-IIIa) compared with 52.3% in those who smoked.[14]

Other studies found modest differences with similar trends. A study conducted in the U.S. states of Hawaii and California found 23.0% of LCINS cases were localized compared with 20.6% in those who smoked.[6] Another study from Hawaii observed 27.5% of LCINS cases were localized compared with 23.8% of cases among those who smoked.[8] On the other hand, one study in Taiwan indicated opposing trends, with only 23.1% of LCINS cases at stages I-III compared with 28.2% among those who smoked.[16]

Sex-based variation in LCINS is not limited to age at diagnosis; women and men also differ in the stage at which they are diagnosed. Among those who have never smoked, the female to male incidence rate ratio for late-stage lung adenocarcinoma was found to be 1.38, equating to a 38% increased incidence of late-stage adenocarcinoma.[19] Another study supported these results, with 92.8% of LCINS cases for women were stage III or IV compared to 85.1% of men.[9]

Risk factors

Air pollution and secondhand smoke

Although robust risk factors for Asian LCINS cases are elusive, many studies have been conducted to evaluate potential candidates. Air pollution, especially particulate matter ($PM_{2.5}$), is a significant health concern in many Asian countries and has therefore been considered a plausible risk factor in LCINS cases among Asian populations.[9,23,32] A study conducted in Taiwan found that for every 10-unit increment of cumulative $PM_{2.5}$ exposure, the risk of lung cancer incidence rose by 1.32-fold and lung cancer mortality rose by 1.28 fold in never smokers.[23] Of note, this increased risk was not found amongst people who had smoked, bolstering the notion that $PM_{2.5}$ exposure is a risk factor specific in the etiology of LCINS.[23] Another study in Taiwan measured $PM_{2.5}$ exposure using daytime visibility data as a proxy and found the same relationship between $PM_{2.5}$ exposure and incidence of LCINS.[32] A cohort observed in Canada indicated $PM_{2.5}$ exposure was significantly higher in persons who had not smoked compared with those who had, and the never-smoker lung cancer cases were disproportionately among Asian persons compared with ever-smokers with lung cancer.[9] Although air pollution appears to be directly related to LCINS case incidence, the study found that secondhand smoke may have an inverse relationship. This same cohort study found that LCINS cases were associated with lower exposure to secondhand smoke.[9] This may be because those who have never smoked are less likely to be in spaces where others smoke, leading to a lowered exposure to secondhand smoke. Although secondhand smoke can be avoided socially, environmental factors such as air pollution may be more difficult to avoid.

It is also important to note that other sources of air pollution, such as burning cooking oils and solid fuels, have previously been reviewed as contributors to LCINS risk.[10,11] The search strategy for this narrative review did not yield new studies on those topics.

Medical comorbidities

The presence of comorbidities has also been investigated. Baseline impaired lung function (measured by spirometry) was associated with increased risk of lung cancer and subsequent mortality for Asian persons who never smoked in Taiwan.[33] More specifically, individuals with preserved ratio impaired spirometry (PRISm), in which an individual's forced expiratory volume in 1 second (FEV1) to forced vital capacity (FVC) ratio is normal despite an impaired FEV1, had a 14% increased risk of lung cancer incidence and 23% increased risk of lung cancer mortality compared with those with normal lung function.[33] Another study in China found asthma history was associated with an increased risk of lung cancer with an odds ratio of 14.720.[34] A study conducted in Japan indicated lymphangioleiomyomatosis (LAM), a rare neoplastic disease that primarily affects young women, significantly increased the risk of lung cancer.[35] A pathway analysis revealed a tuberculosis-related gene set was associated with lung adenocarcinoma and a mendelian randomization study found a positive association between tuberculosis infection and lung adenocarcinoma among Asian women who never smoked.[26]

Telomere length

Telomere length is another potential risk factor for Asian LCINS case incidence. Data from the Shanghai Women's and Men's Health Studies found a dose-response relationship between longer leukocyte telomere length (LTL), genetically-predicted LTL (gTL), and increased lung cancer risk among never smokers in urban China.[36] A similar result was found from a study conducted in Singapore, with a 3.14 times greater risk of lung adenocarcinoma found for individuals in the highest quintile of telomere length compared to the lowest quintile.[37]

Family history

Family history of lung cancer has been shown to be associated with Asian LCINS cases.[15,34,38] In Singapore, Chinese women with a family history, of lung cancer were found to have twice the odds of developing lung cancer compared with those without a pertinent family history.[15] A study from China found that for Chinese individuals who have never smoked and have a family history of lung cancer have more than three times the odds of developing lung cancer compared with those without a family history.[34] Statistically higher odds of developing lung cancer associated with family history were observed among Asian persons who had never smoked and Asian women when compared with Western populations.[38] Results from the TALENT study revealed a significant difference in overall and invasive lung cancer detection with low-dose computed tomography for those with or without a family history of lung cancer.[30] For those with a family history, the lung cancer detection rate was 3.3% and 2.7% for overall and invasive lung cancer, respectively.[30] For those without a family history, the lung cancer detection rate was 2.0% and 1.6% for overall and invasive lung cancer, respectively.[30]

Risk modeling

Efforts in risk modeling have attempted to discover and validate risk factors for lung cancer in populations who have never smoked. A recent study evaluated and designed Asian Lung Cancer Absolute Risk Models (ALARM) for lung cancer mortality.[39] For Asian individuals who never smoked, older age, female sex, personal cancer history, decreased lung function, and history of emphysema or bronchitis were all associated with increased lung cancer risk.[39]

One important dimension of risk modeling involves genetic ancestry and its interaction with mutation prevalence and outcomes. A large cohort of Brazilian lung adenocarcinoma patients found that EGFR mutations were significantly associated with a higher proportion of Asian genetic ancestry, independent of smoking history or self-reported race.[40] In contrast, KRAS mutations were more prevalent among individuals with a lower proportion of Asian genetic ancestry and higher tobacco exposure. These findings suggest that conventional racial classifications may obscure more meaningful biological gradients, and that ancestry-informed genomic stratification may refine current risk models, especially in mixed populations.

Adding further nuance, a meta-analysis showing that a family history of cancer, particularly lung cancer, was significantly associated with somatic EGFR mutations, especially in East Asian populations and never-smokers.[41] Notably, this review of familial case reports identified concurrent germline mutations (e.g., BRCA2, TP53, EGFR T790M) and somatic EGFR alterations in several LCINS cases. These combinations hint at potential germline-somatic interactions in the pathogenesis of EGFR-mutant NSCLC, suggesting dual-layered genomic assessments in high-risk families may further contextualize LCINS risk.

Environmental and epigenetic influences also shape LCINS susceptibility as evidenced in a study that identified distinct DNA methylation patterns in bronchial epithelial cells from never-smokers with lung cancer, pointing to lasting epigenetic alterations linked to environmental exposures and inflammation.[42] These signatures may serve as early biomarkers of carcinogenic transformation in populations not traditionally classified as high-risk, such as young female never-smokers, and may also be leveraged to contextualize LCINS risk and introduce preventative measures like screening.

Meanwhile, another study proposed a polygenic risk score framework for lung cancer in never-smokers, incorporating both common single nucleotide polymorphisms and gene-environment interactions to stratify risk in asymptomatic individuals.[43] Their integrative model highlights the potential of genome-wide association data to guide screening and preventive strategies in traditionally understudied groups.

A study conducted in China further underscored the heterogeneity of LCINS and its multifactorial etiology.[34] Its synthesis of multi-omic data reveals key mutational signatures, including apolipoprotein B mRNA editing enzyme, catalytic polypeptide (APOBEC)-related and air pollution-associated profiles as well as immunologic differences in tumors from never-smokers. This study highlighted how geographic, environmental, and ancestral factors shape distinct molecular phenotypes of LCINS, supporting the incorporation of omics-driven predictors into future risk models.

A complementary study evaluated early-stage EGFR-positive NSCLC patients and revealed high recurrence rates even in stage I disease, despite favorable overall survival.[44] While primarily focused on prognosis, their data support the premise that individual clinicogenomic features (e.g., histologic subtype, co-mutations) are critical for risk stratification and recurrence prediction which reinforces the need for integrated models across the cancer continuum, from risk assessment to treatment selection.

In summary, these studies support a reconceptualization of LCINS not as a monolithic non-smoking disease, but as a spectrum of biologically and demographically distinct subgroups shaped by ancestry, inherited predisposition, and environmental exposures. Risk modeling, especially approaches that combine familial history, ancestry-informative markers, polygenic scores, and epigenetic profiles, may soon enable a more predictive, preventive form of oncology in LCINS.

Protective factors

Dietary fiber and yogurt

In addition to risk factors, researchers have found evidence for potential protective factors for LCINS.

Consumption of dietary fiber and yogurt was shown to be a protective factor, reducing the risk of lung cancer amongst Asian individuals who never smoked.[27] The inverse relationship between fiber and lung cancer was modified by age and alcohol consumption, being strengthened for younger participants and those who consumed more alcohol.[27] The inverse relationship seen for both dietary fiber and yogurt was also reportedly a joint association, with those who reported high yogurt consumption and had the highest quintile of fiber intake saw a 33% reduction in lung cancer risk when compared with those who did not consume yogurt and were in the lowest quintile of fiber intake.[27] Of note, the relationship was also noted to be more evident for those with squamous cell carcinoma. Therefore, current evidence may be insufficient to suggest Asians with lung cancer risk factors increase their fiber or yogurt consumption since adenocarcinoma is the cause of a majority of lung cancer cases among Asian populations.[27]

Body mass index

A higher body mass index (BMI) was found to be a protective factor for individuals who have never smoked in various studies.[25,45] A case control study with four cohorts in the U.S., Europe, China, and Singapore found that individuals who were overweight and obese had a decreased risk for lung cancer, and this relationship persisted even when stratified by smoking status (current, former, and never smokers).[25] Another study of 12 cohorts from the U.S., Europe, and Asia corroborated these results, indicating that individuals with low or normal BMI and high or very high waist circumference had a 40.0% greater risk of lung cancer compared with those with high BMI and normal or moderate waist circumference.[45] It was noted that the inverse association between BMI and non-small cell lung cancer was seen in populations who have never smoked after excluding the first five years of follow-up.[45] However, one pooled analysis of 16 cohorts from North America, Europe, and Asia indicated that BMI associations were not observed when the data was stratified by Asian patients and by individuals who have never smoked.[24]

Given the varied evidence into risk/protective factors and contributors to the etiology of lung cancer in Asian individuals who had never smoked, further research is necessary to elucidate robust risk/protective factors (Table 1). The ascertainment of risk factors becomes important when thinking about "high-risk" populations eligible for potential lung cancer screening efforts.

Screening

Given the epidemiologic patterns described above, including high LCINS incidence in Asian women, younger age of onset, and elevated risk of Asian diaspora populations, screening strategies based solely on smoking fail to capture a substantial proportion of at-risk Asian individuals. Therefore, this narrative review evaluated studies on existing and emerging low-dose CT (LDCT) approaches in the context of these population-specific risk patterns.

Currently, the U.S. Preventive Services Task Force (USPSTF) recommends lung cancer screening with LDCT for adults aged 50–80 years who have a 20 pack-year smoking history and who currently smoke or have quit within the past 15 years.[46] With the rise of lung cancer cases among those who have never smoked, especially among Asian populations, it has become important to reexamine lung cancer screening practices that do not currently capture these populations.

To date, there have been many efforts to build effective lung cancer screening for early diagnosis that leads to better prognosis. The TALENT study was a multi-center LDCT screening trial for never-smoking individuals in Taiwan, which observed a substantial detection rate of 2.6% for lung cancer, and among those diagnosed, 2.1% for invasive lung cancer.[30] These results were notably higher than the detection rate found in the U.S.-based National Lung Screening Trial (NLST) and the European Dutch-Belgian Randomised Lung Cancer Screening Trial (NELSON), which were studies conducted in populations with frequent tobacco use.[30] The high detection rate in individuals without a smoking history highlights the need for lung cancer screening in Asian populations.

In a LDCT screening cohort study of over 50,000 individuals in South Korea, there was a high incidence of subsolid nodule detection in individuals who have never smoked (10.7% in never-smokers vs. 7.7% in ever-smokers), resulting in 227 of 293 (77%) of biopsied subsolid nodules being diagnosed as lung cancer.[28] Another LDCT cohort study in South Korea resulted in 139 biopsied nodules, 84 (60%) of which were diagnosed as lung cancer.[29] Notably, of lung cancer diagnoses made from screening, 75 of 84 (88%) were Stage I.[29] The early detection of lung cancer in asymptomatic individuals whose negative smoking history would have excluded them from screening otherwise supports the importance and health benefit that can result from effective LDCT screening programs.

A LDCT screening program in China resulted in 11.8% (3695 of 31,431) positive baseline LDCT scans and biopsy results found 197 LCINS cases.[47] Importantly, the lung cancer detection rate was highest amongst the high-risk group, with a detection rate of 1.4% and amongst the low-risk group, women exposed to secondhand smoke (SHS) had the highest detection rate of 1.1%.[47] The difference in detection rate when stratifying by risk factors indicated the importance of determining which risk factors are most pertinent for lung cancer development in Asian populations that have never smoked.

Meanwhile, the TALENT study had specific criteria that needed to be met for eligibility (negative chest radiography, aged 55-75, had never smoked or smoked fewer than 10 pack-years and stopped smoking for more than 15 years, with one risk factor, including family history of lung cancer, passive smoke exposure, history of pulmonary tuberculosis or chronic obstructive pulmonary disorders, a cooking index of 110 or higher, or cooking without ventilation) and resulted in the highest lung cancer detection rate amongst Asian persons who have never smoked. Thus its criteria might be considered as foundational for further lung cancer screening efforts.[30]

When evaluating the efficacy of lung cancer screening programs, one must also consider its cost. An evaluation of the cost effectiveness of LDCT screening found that LDCT for individuals who have never smoked was cost effective in Japan, but not in the U.S.[48] The improved lung cancer detection rate seen in the TALENT study as well as the cost effectiveness of LDCT programs in Japan provide multifactorial evidence in support of LDCT screening programs in Asian populations who have never smoked.

As LDCT screening efforts have increased, a growing number of experts have weighed in on their efficacy. A meta-analysis of LDCT screening found that lung cancer diagnosis at baseline was 2.3 times higher among Asians who have never smoked compared with non-Asians.[49] Additional meta-analyses found that the diagnostic rates were higher amongst Asian women who have never smoked and suggested lowering the age of inclusion after finding the average age of diagnosis of individuals who have never smoked was two years younger than those who smoked.[50,51] Experts who analyzed the results found the aforementioned meta-analyses supported the use of LDCT screening for individuals who were deemed higher risk and discouraged its use for lower risk populations.[52] In a letter to the editor, the authors succinctly illustrate the crux of the problem: the evidence may be there, but it is a challenge of awareness and advocacy to support LDCT screening in supposedly low-risk populations.

This is a sentiment that is reflected in many expert opinion reports and screening committees. Consensus among these studies was the issue of overdiagnosis with LDCT screening in which lesions that may never impact a patient's longevity could lead to unnecessary and potentially harmful medical follow-up (i.e., unnecessary invasive biopsy or repeated radiation exposure). Some opinion pieces observed that this risk is worth its potential benefits, citing the results of the TALENT and several other studies that found higher rates of lung cancer amongst Asian populations that have never smoked.[53,54,56] Another report pushes back against LDCT screening, arguing the potential benefits do not outweigh the potential harms and that there have been no randomized controlled trials conducted in those who have never smoked that would definitively assess the benefit and harms of screening.[55] Yet the development of newer imaging technologies such as photon-counting CT scanners (PCCT) offer potential utility for improved lung imaging quality at a significantly lower radiation dose than the conventional energy-integrating detector (EID-CT) system currently used for LDCT screening, underscoring the importance of dynamic discussion regarding risks and benefits of screening.[57] It is also unknown whether the change in the proportion of never-smoker lung cancer may be increasing due to a decreasing denominator rather than an increasing numerator.[58] For both those for and against LDCT screening programs as they currently stand, there is a shared appreciation that more work must be done to improve screening efforts whether that be by strengthening our understanding of risk factors or improvements in screening technology (i.e., computer-aided detection and lowering radiation dosage). Taken together, these studies indicate that LDCT screening in Asian never-smokers is effective, but requires risk models tailored to ancestry, environmental exposure history, and sex-specific patterns identified in our epidemiologic review.

Current treatments and outcomes

Because Asian never-smokers exhibit unique mutation profiles, the therapeutic landscape of LCINS cannot be interpreted without considering ancestry-specific molecular epidemiology.

Treatment strategies and outcomes for LCINS, especially for non-small cell lung cancer (NSCLC), have evolved significantly over the past decade, driven largely by advances in mutation profiling and the development of targeted therapies. This is of particular relevance for LCINS, whose pathogenesis is disproportionately underpinned by oncogenic driver mutations. While standard approaches such as surgical resection and platinum-based chemotherapy remain foundational for early-stage and non-mutated tumors, precision oncology is rapidly redefining the therapeutic landscape. These developments hold particular promise for Asian and Asian American populations, where LCINS is not only more prevalent, but also more likely to involve certain actionable mutations.

Surgical resection

Surgical resection remains a fundamental curative treatment in early-stage lung cancer, especially in NSCLC. In an institutional analysis of over 2,000 resected NSCLC cases, never-smokers were more likely to be younger, female, Asian, and to present with early-stage, low-positron emission tomography (PET)-avidity lower lobe adenocarcinomas.[59] Among stage IA cases, never-smokers also had better overall survival; however, this advantage did not persist in cancer-specific metrics, suggesting the observed benefit may reflect fewer comorbidities rather than intrinsic differences in tumor biology. This is further supported by the lack of any significant differences in five-year disease-free survival or cancer-specific survival between never-smokers and smokers after propensity matching for stage, histology, and other variables. These findings challenge the perception of LCINS as an inherently indolent disease and highlight the persistent risk of recurrence, even in surgically resected cases, particularly relevant for Asian populations, in whom LCINS is increasingly prevalent and may be undertreated under assumptions of favorable prognosis.

Given the high prevalence of actionable mutations in Asian never-smokers, routine mutation profiling alongside resection is increasingly critical. In a cohort of 1,036 pulmonary resections, 647 patients had lung adenocarcinomas that underwent molecular profiling, with 37% of these cases containing EGFR mutations.[60] Excellent outcomes were observed in both EGFR-mutant and wild-type stage I tumors, but among stage II–III cases a trend toward improved survival in EGFR-mutant tumors suggested possible benefit from post-resection intervention. This is supported by the ADAURA trial, which demonstrated significantly prolonged disease-free survival with adjuvant osimertinib in resected stage II–IIIA EGFR-mutant NSCLC. These findings are especially relevant in East Asian populations, in whom EGFR mutations are disproportionately common.[61] Taken together, these findings suggest mutation profiling has a role even in resectable cases in which outcomes are uniformly favorable.

These studies support two seemingly counterintuitive conclusions surrounding surgical resection and mutation profiling. First, even early-stage LCINS which is common among Asian and Asian American populations, should be managed with the same clinical rigor as smoking-related disease, given comparable recurrence risks. Second, mutation profiling should be routine rather than be selectively based on demographic risk factors to enable precision-guided surveillance and identify patients eligible for targeted adjuvant or neoadjuvant therapy alongside resection. As such, while surgical resection remains central to curative management, integrating it within a precision oncology framework is particularly critical in Asian and Asian American patients, where high mutation prevalence warrants routine profiling and, when appropriate, targeted therapy.

Targeted therapy

The therapeutic landscape of LCINS has been transformed by advances in mutation profiling and the emergence of targeted therapies, particularly among Asian populations. Considering the disproportionately high prevalence of driver mutations, such as EGFR, MET, NRG1, ROS1, ALK, and KRAS, among others in this subgroup, targeted therapies have emerged as an effective treatment option in mutation-positive tumors. These personalized approaches not only offer generally improved efficacy and tolerability compared with traditional chemotherapy, but also reflect a broader shift towards precision oncology, addressing the unique burden of key driver mutations in Asian LCINS patients.

EGFR

Among NSCLC patients with EGFR mutations, outcomes following tyrosine kinase inhibitor (TKI) therapy are not uniform suggesting underlying biological heterogeneity not adequately understood, even within this subgroup. In a real-world Canadian cohort of 170 patients with de novo stage IV EGFR-mutant NSCLC receiving first-line TKI therapy, median overall survival was 21 months, but a subset of long-term survivors (≥34 months) emerged.[62] Notably, both never-smoking status and Asian ethnicity were independently associated with improved survival, even after adjusting for metastatic burden and EGFR mutation subtype. Asian patients in particular had a 7-month survival advantage over non-Asian counterparts (25 vs. 18 months), a difference not explained by mutation type, BMI, or access to care. These findings suggest that EGFR-mutant NSCLC in Asian patients may represent a biologically distinct disease, with implications for drug sensitivity, resistance mechanisms, and treatment durability. Such distinctions reinforce the need for routine, comprehensive and further-stratified mutation profiling, especially in high-risk subpopulations like Asian never-smokers, where early identification of targetable alterations can dramatically influence clinical trajectory.

This need for mutation profiling is further contextualized by real-world studies from the pre-osimertinib era, in which, following the failure of first-generation TKIs, treatment options for EGFR-mutant NSCLC were limited. In a 2010–2013 Canadian study evaluating afatinib in EGFR-mutant NSCLC following chemotherapy and first-generation tyrosine kinase inhibitor (TKI) failure, only 25% of patients had confirmed EGFR mutations, yet approximately 40% exhibited disease stabilization or response.[63] Median overall survival was just 5 months. While these findings suggested some pan-EGFR activity for afatinib, they also revealed the diagnostic limitations of earlier mutation testing strategies. Importantly, the study illustrates how presumptive treatment based on clinical features, such as Asian ancestry or never-smoking status, can lead to empiric, often suboptimal therapy. In contrast, contemporary care for Asian and Asian American patients with LCINS demands precise, early, and comprehensive genotyping to optimize TKI selection and maximize survival outcomes.

The introduction of third-generation EGFR inhibitors such as osimertinib has since redefined the first-line standard of care for EGFR-mutant NSCLC. However, resistance inevitably develops, prompting investigation into second-line, multimodal treatment strategies. A 2024 multicenter study from Singapore and Hong Kong evaluated the efficacy of pemetrexed-platinum chemotherapy added to continued osimertinib ("Pem-Plat-Osi") following first-line progression.[64] In this exclusively Asian cohort of 60 patients, the sequential strategy yielded a median overall survival of 34.2 months and central nervous system (CNS) disease control in 90.6% of evaluable patients, including those who had not undergone brain radiotherapy. These findings not only support Pem-Plat-Osi as an effective second-line option but also mark a distinct transition from singular to multimodal targeted therapy in Asian EGFR-mutant LCINS.

Other multimodal treatments have also shown promise post-EGFR TKI progression; the treatment protocol IMpower150 (ABCP: atezolizumab, bevacizumab, carboplatin, paclitaxel) integrates immunotherapy, anti-angiogenesis, and chemotherapy. In the largest reported real-world EGFR-mutant cohort treated with ABCP, clinically meaningful responses were seen even in heavily pretreated patients and those with CNS or leptomeningeal disease.[65] The overall response rate was 52%, with median overall survival of 10.5 months and comparable intracranial response rates in patients with and without prior brain radiation (55% vs. 53%). However, the regimen carried considerable toxicity; 46% required hospitalization, and 50% experienced grade ≥3 adverse events. Given the high burden of CNS involvement and acquired resistance in Asian LCINS patients with EGFR mutations, ABCP represents a viable, if selective, multimodal option following TKI failure, particularly when used in carefully chosen individuals.

Altogether, these studies reflect the increasing complexity of EGFR-mutant LCINS management, particularly among Asian and Asian American patients, who face high EGFR prevalence, elevated CNS risk, and often prolonged treatment courses. While osimertinib remains the frontline standard, real-world Asian cohort data on sequential regimens like Pem-Plat-Osi and broader strategies such as ABCP show that survival can be meaningfully extended when escalation is timely and individualized. Crucially, these findings reaffirm the importance of comprehensive and timely mutational profiling and reprofiling, enabling precision-guided therapy that accounts for evolving tumor biology, resistance dynamics, and population-specific treatment considerations.

Other mutations and multiple mutations

Though EGFR is among the more-prominent mutations involved in Asian LCINS patients, a growing set of other mutations contribute to the disease's heterogeneity, many of which also show Asian-specific enrichment. ROS1 rearrangements, for example, though rare overall (~1–2% of NSCLC), are observed in 2–3% of East Asian populations. In a study of 35 Chinese patients with proto-oncogene tyrosine-protein kinase ROS (ROS1)-rearranged NSCLC, nearly all never-smokers, treatment with crizotinib yielded a 71.4% response rate and median overall survival of 41 months.[66] However, its limited CNS penetration and vulnerability to resistance mutations (e.g., glycine-to-arginine substitution at codon 2032 or G2032R) constrain long-term efficacy.

Newer agents such as taletrectinib aim to address these limitations. In the TRUST-I trial of 173 Chinese patients with ROS1-rearranged NSCLC, taletrectinib demonstrated a 91% response rate in TKI-naïve patients, 52% in crizotinib-pretreated patients, and strong CNS activity, including against G2032R.[67] These results affirm taletrectinib's potential as a next-generation ROS1-targeted agent for Asian LCINS populations.

A similarly successful paradigm has been observed in anaplastic lymphoma kinase (ALK)-rearranged NSCLC, which is enriched among Asian never-smokers with adenocarcinoma histology. In a cohort of 148 ALK-positive patients, 76% of whom were never-smokers, first-line alectinib produced durable responses, with 57% progression-free survival at both 2 and 3 years and median overall survival exceeding 54 months.[68] Access to multiple ALK inhibitors has enabled long-term disease control through sequential therapy, even in cases requiring dose adjustments or switching due to toxicity. These findings reinforce ALK rearrangement as a prime example of effective, multi-line targeted therapy in LCINS.

By contrast, other mutations such as MET exon 14 skipping, NRG1 fusions, and KRAS mutations remain more therapeutically challenging. METex14 alterations, frequent in older, never-smoking patients, are associated with shorter survival (median 12 months) and low response rates (~28–30%) across therapies.[69] Similarly, NRG1 fusions, enriched in never-smokers, respond poorly to both chemotherapy and pan-ERBB inhibitors like afatinib.[70] KRAS mutations, though less common in East Asians, demonstrate variable treatment responses: in a Taiwanese cohort, immune checkpoint inhibitors produced a modest 21.7% response rate, largely confined to PD-L1–high tumors.[71] Collectively, these findings stress the therapeutic gap that persists for less-characterized alterations in Asian LCINS populations, where few effective options exist beyond the EGFR/ALK/ROS1 axis.

Beyond the more frequently studied alterations in LCINS, a growing body of evidence supports the clinical relevance of rarer, yet actionable, mutations in Asian never-smokers. B-Raf proto-oncogene (BRAF) V600E mutations, which are present in ~2% of NSCLC, have demonstrated responsiveness to dabrafenib-trametinib combination therapy. A case report of an Asian never-smoker with advanced refractory disease showed rapid tumor regression and symptom relief, consistent with broader non-randomized trial data.[72] Similarly, an isolated case of platelet-derived growth factor receptor alpha (PDGFRA) N848K mutation, a mutation best characterized in gastrointestinal stromal tumors, responded durably to imatinib in an Asian female never-smoker.[73] Although anecdotal, these examples highlight the value of comprehensive genomic profiling in detecting rare, targetable alterations in this high-prevalence population.

Rarer still, and more complex, are cases involving multiple concurrent oncogenic mutations. While most mutation-driven therapies assume a single dominant driver, emerging evidence suggests that some patients harbor de novo combinations of actionable mutations that influence treatment response and resistance dynamics. One report described a never-smoking patient with concurrent EGFR exon 19 deletion and MET amplification who initially progressed on gefitinib but achieved marked response with added crizotinib.[74] These findings suggest dual-targeted approaches may benefit patients with compound oncogenic drivers, particularly in Asian LCINS, where such overlap may be underrecognized.

In summary, the therapeutic landscape of LCINS has become increasingly defined by mutational stratification, particularly among Asian populations where the prevalence of targetable driver mutations is high. While established alterations such as EGFR, ALK, and ROS1 have well-validated treatment algorithms, other mutations, including MET, NRG1, KRAS, BRAF, and PDGFRA, demonstrate more variable responses and less mature clinical guidance. The identification of rare or co-occurring mutations, such as concurrent EGFR mutation and de novo MET amplification, further complicates treatment selection and highlights the limitations of single-agent targeted approaches in certain subsets. These findings accentuate the ongoing need for comprehensive mutation profiling at diagnosis and progression, as well as for continued clinical investigation into rare and compound alterations. As insights into the mutational profiles of LCINS expand, treatment paradigms will need to adapt to accommodate increasingly heterogeneous genomic contexts, tailoring interventions not only to mutation type, but to the population-specific disease context in which they arise.

Immunotherapy

In parallel with targeted therapies, the emergence of immune checkpoint inhibitors (ICIs), particularly those targeting the PD-1/PD-L1 axis, has also transformed the treatment landscape of advanced NSCLC. Among these, atezolizumab, an anti–PD-L1 agent, and PD-1 inhibitors such as pembrolizumab and nivolumab have demonstrated improved survival outcomes across diverse patient subgroups. However, their efficacy is modulated by several clinical and molecular features that are especially relevant to Asian never-smokers with LCINS.

A meta-analysis of 4,859 patients across seven randomized trials found that atezolizumab significantly improved survival and progression-free survival compared to chemotherapy, particularly in patients with wild-type EGFR, a smoking history, and high PD-L1 expression.[75] In contrast, no survival benefit was observed in never-smokers or patients with EGFR mutations, characteristics disproportionately represented in Asian LCINS populations. While PD-L1 expression emerged as a useful biomarker, its predictive value was greatest in high expressors, a subgroup that may be underrepresented among Asian never-smokers, many of whom harbor EGFR mutations and tend to exhibit lower tumor mutational burden.

Similarly, a meta-analysis of 11 trials involving 5,887 NSCLC patients treated with PD-1 inhibitors showed broad survival benefit across several subgroups.[76] However, EGFR-mutant patients again showed no significant advantage with PD-1 monotherapy, particularly those with low to intermediate PD-L1 expression. These findings reinforce the growing consensus that ICI monotherapy offers limited benefit in EGFR-mutant or never-smoking populations, highlighting the need for combination strategies or alternative therapies in these populations with significant Asian overlap.

These findings demonstrate that while ICIs confer meaningful benefit in advanced NSCLC, their efficacy varies substantially by molecular and clinical features. PD-L1 expression remains the most reliable biomarker to guide treatment selection, though smoking status, EGFR mutation status, and metastatic burden also modulate response. For patients with high PD-L1 expression, monotherapy may suffice; for others, particularly those with lower PD-L1 expression, EGFR mutations, or liver metastases, combination regimens or alternative strategies may be warranted.

Beyond precision oncology

While mutation profiling and precision therapies have reshaped the treatment landscape of LCINS, particularly among Asian never-smokers, population-level data reveal persistent implementation gaps that blunt the impact of these advances. A single-institution study from Tufts Medical Center comparing Asian and White lung cancer patients, including never-smokers, found that Asian patients were more likely to present with late-stage disease, experience delayed time-to-treatment initiation (TTI), and forgo cancer-directed therapy altogether.[77]

These disparities persisted even in early-stage cases, in which median TTI for Asian patients exceeded that of White patients by nearly a month. Despite these barriers, overall survival was not inferior and was likely due to the higher prevalence of targetable mutations, particularly EGFR, and the broader use of targeted therapies. Nevertheless, such favorable outcomes may obscure underlying system-level failures in early detection, care navigation, and access to precision therapies.

Complementing these findings, substantial improvements in median overall survival, from 15.5 to 24.9 months for Asians with LCINS, have been driven in part by broader access to EGFR TKIs and pemetrexed.[17] The improved prognosis among never-smokers was not attributable to earlier-stage diagnoses; in fact, more never-smokers presented with stage IV disease. Rather, survival gains were concentrated in patients receiving mutation-directed therapies. These findings reinforce that LCINS, especially in Asian populations, is not only biologically distinct but also increasingly clinically manageable provided diagnostic and therapeutic advances are equitably implemented.

Altogether, the evolving treatment paradigm for LCINS, particularly among Asian populations, runs in parallel with the emergence of precision oncology. Surgical resection remains foundational for early-stage disease, but its role must now be contextualized within a genotypically informed framework that integrates routine mutation profiling and, where indicated, adjuvant targeted therapies. For advanced-stage disease, the proliferation of genotype-directed agents, most notably EGFR, ALK, and ROS1 inhibitors, has redefined survival expectations, while new strategies continue to emerge for rarer or co-occurring mutations. Yet, despite these advances, immunotherapy remains variably effective in LCINS, and many mutational profiles still lack durable treatment options or clear clinical guidance.

Cumulatively, these studies articulate a dual imperative to continue advancing the science of precision treatment in LCINS and to close the care delivery gaps that limit real-world impact. As the incidence of LCINS among never-smokers continues to rise, particularly in Asia and among Asian diaspora populations, both precision oncology and public health infrastructure must evolve in tandem to realize the full potential of current therapies. The path forward lies not only in advancing molecular insights, but in equitable access, timely diagnosis, and system-wide capacity to deliver individualized care. Bridging that divide will be essential to realizing the full promise of precision oncology in Asian LCINS patients.

Future targets

The future of LCINS management in Asian populations depends on expanding the catalog of targetable alterations and improving access to accurate, ancestry-informed diagnostics. These advances are critical for addressing the gaps identified earlier in epidemiology, screening, and treatment.

Despite substantial advances in the treatment of NSCLC, patients with LCINS, particularly those of Asian ancestry, continue to face a fragmented and often-delayed path to precision care. While EGFR and ALK-targeted therapies have marked a turning point in the management of mutation-positive tumors, these benefits remain limited to a subset of patients. Even among those with targetable mutations, critical barriers persist, including inconsistent genomic testing, delayed diagnoses, and inequitable access to therapies.

Even among mutation-positive patients, persistent gaps in testing, delayed diagnoses, and uneven access to targeted treatments remain critical barriers in real-world outcomes for LCINS among Asian populations. Recent genomic, transcriptomic, and proteomic studies have begun to illuminate this subgroup, revealing novel mechanisms such as estrogen receptor signaling, chromatin remodeling, and environmentally influenced mutational signatures. At the same time, advances in biomarker discovery, family-based risk stratification, and molecular diagnostics are expanding the possibilities for early detection and personalized intervention.

This section highlights two emerging domains shaping the next generation of LCINS care: (1) the expansion of mutational targets from traditional EGFR- and ALK-mutant tumors to co-occurring mutations not currently addressed by standard therapies; and (2) diagnostics, developing the tools and technologies enabling more accurate, earlier, less-invasive, and population-tailored detection. Together, these strategies reflect a broader shift toward stratifying oncological heterogeneity and implementing earlier interventions, particularly in underrepresented subpopulations like Asian never-smokers.

Expanding mutational targets

Although EGFR and ALK have historically dominated the targeted therapy landscape in Asian patients with LCINS, approximately 20–30% of cases lack these canonical drivers. Even among EGFR-positive patients, real-world data increasingly highlights the clinical significance of rare and compound mutations not addressed by standard TKI regimens. This growing oncological heterogeneity has solidified the need to broaden mutation-guided therapeutic strategies in Asian populations beyond conventional targets.

The study of a large Indian cohort found that nearly 15% of EGFR-mutant NSCLC cases harbored uncommon mutations, with another 7.6% exhibiting compound alterations, most commonly G719X paired with exon 19 deletion or exon 20 S768I.[78] These mutations, though less prevalent, were associated with improved survival following TKI therapy, supporting their inclusion into routine mutation profiling in this subgroup.

A similar study demonstrated substantial variation in TKI response across uncommon EGFR subtypes, including exon 20 insertions and compound T790M mutations using both *in vitro* and patient-derived xenograft models.[79] These results reinforce the case for mutation-specific treatment selection over uniform therapeutic algorithms, particularly in TKI-refractory or EGFR-wildtype tumors, and further emphasize the role of comprehensive genomic profiling in guiding individualized care.

Beyond EGFR, non-canonical alterations such as rearranged during transfection (RET) rearrangements are also emerging as relevant therapeutic targets. A study from Singapore reported that Asian patients with RET-rearranged tumors receiving selective RET inhibitors experienced significantly longer overall survival, especially among those with CCDC6-RET fusions.[80] The study also uncovered significant discordance between fluorescence in situ hybridization (FISH) and next generation sequencing (NGS)-based RET testing, highlighting the need for standardized, high-sensitivity diagnostics.

Moving forward, these studies reflect a growing shift from a narrow focus on canonical drivers to a broader framework that incorporates rare, compound, and non-EGFR alterations. As the catalog of targetable mutations expands, too does the potential for truly personalized treatment paradigms that are tailored not only to specific mutations, but to the full molecular complexity of each patient's tumor.

Diagnostics

As precision oncology continues to reshape LCINS management, diagnostic paradigms are evolving beyond conventional histology and limited gene panels, developments especially critical for Asian never-smokers who remain underrepresented in clinical trials yet disproportionately affected by actionable mutations.

One study demonstrated that companion diagnostics (CDx) significantly improved survival in non-squamous NSCLC, with a median of 13.0 versus 6.0 months and a 28% reduction in mortality risk.[81] Notably, Asian and never-smoking patients were more likely to receive CDx which reflected clinical awareness of their higher mutation burden. However, testing uptake remains inconsistent across settings, revealing gaps in implementation despite clear prognostic and therapeutic value.

The diagnostic blind spots affecting LCINS patients are further highlighted in a study which found EGFR mutations in 8.8% of patients diagnosed with squamous histologies based on small biopsies, most of whom were never-smokers and women, overlapping with the conventional Asian LCINS profile.[82] Notably, subsequent surgical specimens often revealed adenosquamous carcinoma, a histologic subtype frequently misclassified in small biopsies. The results of this study support routine EGFR testing even in tumors initially classified otherwise, particularly among Asian never-smokers, to avoid underdiagnosis of actionable mutations. Without routine EGFR testing, especially in ambiguous or squamous-predominant presentations, this patient population risks being systematically excluded from targeted therapies.

Efforts to increase test sensitivity and tumor representativeness are further supported by a study that evaluated a hybrid DNA/RNA NGS panel that significantly increased actionable mutation detection compared with DNA-only panels.[83] In the context of limited tissue or challenging histologies, RNA-based fusion detection proved especially valuable, highlighting the need for diagnostic platforms capable of capturing complex or rare alterations. A similar study advocated for multiomic integration and the inclusion of RNA-based assays, which may enhance fusion gene detection and offer transcriptomic insights previously inaccessible in routine diagnostics.[84]

Finally, the clinical and economic case for incorporating NGS in Asian practice settings is exemplified by real-world data from Singapore. In a cost-effectiveness analysis of patients with non-squamous NSCLC, researchers found that upfront NGS identified additional actionable alterations with minimal added cost and faster turnaround time compared to sequential testing.[85] These findings are especially relevant in EGFR-predominant Asian populations, in which tissue limitations and molecular heterogeneity challenge traditional diagnostic workflows. While academic centers have led NGS adoption, uptake in community settings remains inconsistent, highlighting the need for policy and operational reforms to standardize access to molecular diagnostics and realize the full potential of precision oncology in LCINS.

Taken together, these studies reinforce that diagnostic equity is not only a technical issue, but a population-level one. For Asian never-smokers with LCINS, who often harbor actionable but under detected mutations, the promise of precision medicine depends on expanding both the reach and representativeness of diagnostic platforms across healthcare systems.

CONCLUSION

In conclusion, lung cancer in people who have never smoked, particularly across Asia and the Asian diaspora, represents an increasingly recognized disease subtype that diverges from conventional smoking-centric models of lung cancer etiology and care. Across diverse studies, Asian never-smokers have been found to exhibit elevated incidence rates, a predominance of adenocarcinoma histology, and a high prevalence of actionable driver mutations such as EGFR, ALK, and ROS1. These patterns point to a confluence of genetic, environmental, and inherited factors that are insufficiently captured by traditional risk prediction models used to identify potentially eligible screening candidates.

The continued reliance on aggregated racial and ethnic categories, such as the broad "Asian or Pacific Islander" classification, further obscures important differences between subpopulations. While much of the current literature reports elevated mutation prevalence and treatment response among "Asian" patients, this umbrella term conceals meaningful heterogeneity in genetic ancestry, environmental exposures, cultural practices, and health system access across East Asian, Southeast Asian, and South Asian populations. Parsing these subpopulations more precisely, both genetically and socio-demographically, is essential for refining risk models, improving screening eligibility, and tailoring treatment strategies. At the same time, efforts to disaggregate Asian subpopulations must be approached with care to avoid reinforcing stigma or implying biological essentialism. The goal is to recognize meaningful heterogeneity in ways that improve equity and clinical relevance, while ensuring that subgroup differences are interpreted within social, environmental, and structural contexts rather than as fixed attributes of racial or ethnic identity. As such, the future of LCINS research and clinical care will require disaggregated data that respects and reflects the complexity of Asian ancestry identities and lung carcinogen exposures.

Efforts to implement low-dose CT screening in never-smokers, while promising in East Asia, remain limited by overdiagnosis concerns, cost-effectiveness debates, and lack of consensus on risk thresholds. Risk models that incorporate sex, comorbidities, lung function, ancestry, and family history represent promising tools for refining eligibility, but have not been widely adopted and remain limited in scale. New technologies such as photon-counting CT provide a possibility for screening methodology with improved resolution and lowered amounts of radiation compared with conventional methods used with low-dose CT.[57] To maximize benefit and minimize harm, screening must move beyond static criteria toward innovative, population-informed approaches.

On the therapeutic front, precision oncology has radically reshaped the treatment of LCINS, particularly among Asian never-smokers with high rates of actionable mutations. Yet this transformation remains uneven. While front-line osimertinib and next-generation ALK and ROS1 inhibitors have extended survival in select groups, treatment options for rare, compound, or non-canonical mutations are limited and often off-label. Immunotherapy, while a pillar in other NSCLC subsets, has demonstrated mixed efficacy in LCINS, particularly among EGFR-mutant or low-PD-L1 tumors.

Future directions will hinge on two interconnected imperatives: deepening molecular insight and expanding real-world implementation. Advances in genomics, transcriptomics, and multi-omic diagnostics are enabling the identification of increasingly rare alterations, but these insights must be matched by equitable access to testing, timely diagnosis, and treatment delivery. Particularly in underrepresented populations such as Asian never-smokers, who face delayed treatment and diagnostic disparities even in high-resource settings, precision must not stop at the bench or bedside, it must extend to policy, practice, and population health.

Ultimately, LCINS in Asian populations sits at the intersection of scientific opportunity and structural challenge. Bridging the gap between innovation and access will require not only more-inclusive science, but also more granular data, equitable infrastructure, and a deliberate move toward disaggregated, subpopulation-informed approaches to care. Only then can the full promise of current and emerging practices be realized for LCINS patients, across the full diversity of those it aims to serve.

By integrating epidemiology, environmental exposures, ancestry-informed risk modeling, screening performance, and mutation-driven therapeutics across Asian populations in Asia and the diaspora, this review proposes a cohesive framework for understanding LCINS as a heterogenous, ancestry-environment interaction disease. This perspective sought to clarify why smoking-based paradigms fail for Asian populations and highlights the need for precision screening, diagnostics, and care pathways tailored to the specific biologic and demographic profiles of these communities. The purpose of this synthesis is to posit a roadmap for future research and policy aimed at delivering equitable, population-specific precision oncology for Asian never-smokers worldwide.

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Supplemental Material

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