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Lung cancer in patients who have never smoked — an emerging disease

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Abstract

Lung cancer is the most common cause of cancer-related deaths globally. Although smoking-related lung cancers continue to account for the majority of diagnoses, smoking rates have been decreasing for several decades. Lung cancer in individuals who have never smoked (LCINS) is estimated to be the fifth most common cause of cancer-related deaths worldwide in 2023, preferentially occurring in women and Asian populations. As smoking rates continue to decline, understanding the aetiology and features of this disease, which necessitate unique diagnostic and treatment paradigms, will be imperative. New data have provided important insights into the molecular and genomic characteristics of LCINS, which are distinct from those of smoking-associated lung cancers and directly affect treatment decisions and outcomes. Herein, we review the emerging data regarding the aetiology and features of LCINS, particularly the genetic and environmental underpinnings of this disease as well as their implications for treatment. In

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Author contributions

All authors researched data for the article and contributed substantially to the discussion of content. J.L. wrote the article. All authors reviewed and/or edited the manuscript before submission.

Competing interests

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addition, we outline the unique diagnostic and therapeutic paradigms of LCINS and discuss future directions in identifying individuals at high risk of this disease for potential screening efforts.

Introduction

Lung cancer is the leading cause of cancer-related death worldwide (see GLOBOCAN) and in every ethnic group in the USA[1]. Smoking-related lung cancers account for the majority of lung cancer diagnoses and continue to claim ~100,000 lives in the USA each year[1]; however, smoking rates have been decreasing for several decades. Although varying widely across the USA, cigarette smoking prevalence among adults reached an all-time low at 11.5% in 2021 (ref. 2), down by more than two-thirds (from ~42%) since the first Surgeon General's Report linking cigarette smoking to lung cancer and heart disease in 1964 (ref. 3) (Fig. 1a) and is projected to fall further to 7.5% overall by 2065 (ref. 4). As smoking prevalence has declined, some reports indicate that the proportion of lung cancers occurring in individuals who have never smoked (LCINS) has increased, particularly among women and in younger age groups[5]. In 2023, >20,000 lung cancer-related deaths in the USA were projected to occur in people who have never smoked[1], making LCINS the eighth leading cause of cancer-related mortality in the USA; data suggest that LCINS is currently the fifth most common cause of cancer-related deaths worldwide[6] (Fig. 1b).

LCINS have histological and epidemiological distinctions from smoking-related lung cancers given that they are almost exclusively adenocarcinomas and most commonly occur in women and individuals of Asian ancestry[7,8]. Moreover, several studies have revealed that LCINS are also genomically and molecularly distinct from smoking-related lung cancers, highly enriched for targetable oncogenic alterations (such as *EGFR* mutations or *ALK* rearrangements as well as less common alterations), and thus often require different diagnostic and therapeutic strategies. Over the past decade, new data have emerged regarding the genetic risk of LCINS, conferred by both common and rare germline variants, as well as environmental risk factors and potential interactions between the two. Conceivably, LCINS could eventually become the most common form of lung cancer, necessitating a thorough understanding of its pathogenesis and risk factors. Herein, we review the epidemiological, clinical and genomic features of LCINS, along with data from studies examining both genetic and environmental risk factors, as well as diagnostic and treatment strategies.

Definitions

In an effort to mitigate the stigmatization of patients with lung cancer, the International Association for the Study of Lung Cancer released a language guide in 2021 that includes replacing the term 'smoker' with language such as 'person who has smoked', and 'never-smoker' with 'person who has never smoked'[9]. Definitions of smoking status have varied; however, the Centers for Disease Control and Prevention and others have previously used the term 'never-smoker' (or sometimes 'non-smoker') to refer to individuals who have smoked <100 cigarettes in their lifetime, and LCINS is defined as lung cancer arising in such individuals. The previously used terms 'former smoker' or 'ex-smoker' are defined as

people who have smoked >100 cigarettes in their lifetime but quit smoking ≥12 months prior to a lung cancer diagnosis. The term ‘long-term former smoker’ has been used to refer to those who have smoked >100 cigarettes in their lifetime but quit smoking ≥15 years prior to a lung cancer diagnosis, and individuals with ‘remote’ smoking histories include those who smoked infrequently and/or socially as adolescents and/or young adults but still smoked >100 cigarettes in their lifetime; both of these categories might share certain characteristics with those who have never smoked. A current smoking status refers to individuals who have smoked >100 cigarettes in their lifetime and who still report smoking every day or some days. Nevertheless, data from several studies suggest that smoking history should be quantified as a continuous rather than discrete variable, supported by findings such as the likelihood of a lung adenocarcinoma (LUAD) harbouring an *EGFR* mutation decreasing as number of pack-years increases[10]. As discussed below, the discovery of tumour mutational signatures corresponding to tobacco smoking might eventually help to delineate what constitutes a clinically significant level of exposure from a genomic perspective.

Epidemiology

Approximately two-thirds of LCINS cases occur in women, making women who have not smoked more than twice as likely to develop lung cancer than men who have not smoked[5,11]. The proportion of lung cancers attributable to tobacco smoking varies across countries, at >80% in men and women in the USA and the UK[12–14], and 57.5% in men and 13% in women in China[15]. A never-smoking status is more frequent among female patients in Asia than those in other regions and, interestingly, >55% of female Asian patients and >30% of Hispanic female patients diagnosed with non-small-cell lung cancer (NSCLC) in the USA have never smoked[16]. However, even when compared specifically with non-smoking women in other geographical regions, lung cancer incidence rates have been observed to be higher among women in East Asia[17], suggesting that genetic and/or environmental factors other than tobacco smoke exposure contribute to the global variation in the prevalence of LCINS.

The average age at LCINS diagnosis is similar to that reported for smoking-related lung cancers[5] (median age at diagnosis of 67 years versus 65 years; $P = 0.1$)[7], although younger patients with lung cancer are more likely to have never smoked. In a study including 121 patients <40 years of age at diagnosis and with a documented smoking history, 73% had never smoked; 90% of these patients had LUAD, >80% of which harboured a targetable oncogenic alteration[18]. Patients with *ALK*-rearranged NSCLC, which mostly occurs in individuals who have never smoked, are younger on average at diagnosis (median age at diagnosis 50–52 years)[19–22], as are patients with other LUADs harbouring oncogenic fusions, for example, involving *RET*[23,24], *ROS1* (refs. 22,25–27) or *NTRK1–3* (ref. 28).

In economically developed countries, smoking prevalence has decreased among all age groups (in the USA, most steeply amongst those <30 years old in the USA), reflected in an overall decreasing incidence of lung cancer[1,29]. Lung cancer incidence is decreasing twice as fast in men than in women, and perhaps four times as fast, based on an analysis of United States Cancer Statistics data[30] examining annual percentage change in NSCLC incidence[31,32] over 2001–2019 (J.L. et al., unpublished data), a difference that is only

partially explained by differences in smoking trends[33–35]. Notably, the incidence of lung cancer is now higher in women than in men in both Hispanic and non-Hispanic white individuals born during or after the mid-1960s whereas, prior to this time, the incidence was higher in men than in women[35]. This pattern is also expected to reverse (that is, lung cancer incidence will become higher in women than in men) in the remaining birth cohorts by 2045 if current smoking trends continue[4]. Trends in NSCLC histology also reflect the decreasing smoking prevalence, with a relative increase in LUAD and decrease in lung squamous cell carcinoma (LSCC) over time[36,37].

Precise national and global trends in LCINS epidemiology are unavailable owing to a lack of individual-level data on smoking status, which historically has not been collected in cancer registries or on death certificates. However, a retrospective study including >10,000 patients from three independent cancer centres revealed that the proportion of LCINS relative to total NSCLC diagnoses increased from 8.0% in 1990–1995 to 14.9% in 2011–2013 ($P < 0.001$)[5]. This trend was independent of sex, disease stage at diagnosis and ethnicity, and no statistically significant increase in the proportion of LCINS was observed among small-cell lung carcinoma (SCLC) or LSCC diagnoses[5]. However, additional and contemporary data are needed to determine true trends in LCINS epidemiology.

Features of LCINS

In addition to histological characteristics shared among LCINS, genomic and molecular features have been more recently characterized in LCINS as compared to lung cancers occurring in patients with a history of smoking. The findings underscore the distinct biology of LCINS, with important diagnostic and treatment implications (Table 1).

Histology

As noted above, LCINS are near-exclusively LUADs[5,16] and largely driven by oncogenic alterations in key pro-survival signalling pathways. Although LUAD accounts for a substantial number of smoking-related lung cancers, both LSCC and SCLC are more strongly associated with smoking and typically arise in the larger, central airways that are more readily accessible to tobacco smoke. An estimated 6–8% of LSCCs and SCLCs occur in patients who have never smoked[16], and the age-adjusted odds ratios (OR) for LUAD, LSCC and SCLC development in men who currently smoke are 21.9, 103.5 and 111.3, respectively[38–40]. An analysis of 11 cases of SCLC diagnosed in individuals with a history of former light smoking or never smoking revealed that most tumours (8 of 11; 73%) were of mixed histology or non-pulmonary origin[41]. Furthermore, driver mutations were detected in *EGFR, NRAS, KRAS, BRCA1* and *ATM*, and one tumour had a *TMPRSS2–ERG* fusion[41]. These findings suggest that SCLC arising in those who have never smoked constitutes a distinct disease entity, requiring different therapeutic approaches than smoking-related SCLC.

LUADs occurring in the presence or absence of tobacco smoke exposure are largely similar in histological appearance and typically cannot be distinguished based on histological subtype or features when adjusted for pathological stage; differences in adverse prognostic features, such as lymphovascular invasion, visceral pleural invasion and spread of tumour

through airways, have not been reported. However, cigarette smoking is strongly associated with the presence of a solid component within the tumour (prevalence of 53% versus 20% in stage I LUADs from individuals who had never smoked; multivariate HR 3.32, 95% CI 1.78–6.19; $P < 0.001$), and *EGFR*-mutant LUADs less frequently contain solid components than *EGFR*-wild-type LUADs (17% versus 51%; $P = 0.033$)[42]. Most studies have not characterized histology beyond LUAD and LSCC, although one study of 320 stage I LUADs revealed that those in patients with a never-smoking status are more frequently bronchioalveolar carcinoma (85% versus 58% in ever-smoking patients; $P < 0.001$) and more commonly have papillary components (81% versus 68%; $P = 0.01$)[42]. No histological differences in precursor lesions between never-smoking and ever-smoking patients have been reported, such that adenocarcinoma in situ in a never-smoking patient is indistinguishable from that occurring within the context of a field effect in a patient who has smoked; however, some evidence indicates that adenocarcinoma in situ and minimally invasive adenocarcinoma in patients with a history of smoking tend to be larger than those in patients who have never smoked[43]. Features including a signet ring cell morphology, cribriform formation and solid or acinar growth patterns have been associated with *ALK*-rearranged LUAD[44–49]; similar features have been identified in LUADs harbouring *ROS1* or *RET* fusions[50].

Imaging characteristics

Several studies have examined various radiographical features of molecular subtypes of LUAD and, in general, radiographical differences correlate with the molecular driver and not with smoking status. Fusion-positive LUADs often have striking solid components, corresponding to areas of invasiveness on histology[51–53]. In one study, *ALK*-rearranged LUADs tended to be centrally located, associated with large pleural effusions and lacking a pleural tail[54]. No characteristic imaging findings have been consistently identified in *KRAS*-mutant or *EGFR*-mutant LUADs, and conclusions have been confounded by differences in image acquisition, cancer stage and geographical location (that is, East Asian versus non-Asian cohorts)[55–57]. However, characteristic volumetric tumour response dynamics have been observed following treatment with EGFR tyrosine kinase inhibitors (TKIs), consisting of an initial marked decrease in tumour burden followed by a slower decrease until the point of maximal response[58–62]. The magnitude of the initial, and thus the maximal, response is predictive of survival duration in patients receiving EGFR TKIs[58], and slower rates of tumour regrowth following maximal response are associated with longer overall survival (OS)[63]. Although not clinically useful at this time, radiomic machine learning algorithms using multimodal imaging features might eventually aid in determining the molecular driver present in an individual NSCLC[57,64,65].

Patterns of metastatic disease

Certain patterns of metastatic spread also correlate with the molecular driver. Among patients with NSCLCs harbouring *EGFR* mutations or *ALK* rearrangements, 50–60% present with or eventually develop brain metastases, compared with 16–20% of unselected patients with NSCLC[66–74]. *ROS1*-rearranged LUADs are associated with roughly half this frequency of brain metastasis (~36%), although estimates vary widely owing to the relative rarity of this disease subtype[22,25,75]. With the advent of osimertinib – a third-generation,

brain-penetrant EGFR TKI – the risk of developing brain metastasis while on treatment has been observed to be three times less than with earlier-generation TKIs[76].

Oncogenic driver alterations

Constitutive activation of a growing number of oncogenes through mutation, rearrangement and/or amplification accounts for 78–92% of LCINS versus 49.5% of smoking-related LUADs[7,40] (Fig. 2). The most common genetic alterations include mutations in *EGFR, KRAS, HER2, MET* and *BRAF*, rearrangements involving *ALK, ROS1, RET* and *NTRK1–3*, and *MET* amplification, and prevalences of these alterations vary according to age and genetic ancestry (for example, East Asian versus non-East Asian)[77] as well as according to heterogeneity of the molecular testing assays used. Somatic sequencing studies include those at the whole-exome[7] (Fig. 2a) and whole-genome[78] (Fig. 2b) levels, as well as panel-based next-generation sequencing (NGS) data derived from the AACR Project GENIE cohort, which is the largest collective somatic sequencing study in patients with cancer and comprises clinical data from multiple institutions. A subset of the AACR Project GENIE cohort (Biopharma Collaborative NSCLC cohort[79], n = 1,846) has been annotated for outcomes and clinicopathological variables, including smoking status, providing insights on the prevalence of oncogenic alterations in LUADs from patients who have never smoked (Fig. 2c). Rare molecular subtypes of lung cancer, most of which are more commonly found in LCINS, have been recently reviewed in this journal[80].

EGFR.—*EGFR*-mutant LUAD constitutes the largest proportion of LCINS, with rates as high as 60–74% in non-smoking East Asian women with lung cancer[77]. RNA sequencing (RNA-seq) and whole-exome sequencing (WES) data from a large cohort of never-smoking patients with LUAD (n = 160) found *EGFR* to be mutated in up to 52.5% of participants (versus ~10.4% of smoking-related LUADs)[7]. Canonical mutations in exons 19 and 21 (that is, exon 19 deletions and the L858R point mutation, respectively) account for the vast majority of *EGFR* alterations in LCINS (>85%), without a preponderance of one alteration relative to the other[7], although the L858R mutation and exon 19 deletions seem to occur more frequently in older and younger patients, respectively[18,81]. *EGFR* mutations occur in a small fraction of smoking-related lung cancers, with the likelihood of *EGFR* mutation decreasing with increasing pack-years[10]. Regardless of pack-years smoked, the likelihood that a lung cancer will harbour an *EGFR* mutation increases with the number of smoke-free years prior to diagnosis, particularly in those who have stopped smoking for >25 years[10,82].

Uncommon sensitizing and non-sensitizing *EGFR* mutations might be more likely to occur in smoking-related compared with non-smoking-related lung cancers[83,84]; however, ~60% of patients with uncommon *EGFR* exon 20 insertions have never smoked and most are women, in contrast to those with *EGFR*-wild-type cancers (but similar to those with classical sensitizing *EGFR* mutations)[84–87]. In a study of 102 NSCLC samples harbouring uncommon *EGFR* mutations, 85% of those with exon 18 alterations and 43% of those with exon 20 alterations occurred in patients with a history of smoking[84]. Rarely, oncogenic *EGFR* fusions occur, most commonly with *RAD51* as the fusion partner, and reports of *EGFR–RAD51* fusions in LUAD most often involve patients with a history of never or light (<5 pack-year) smoking, who are mostly young (<40 years of age)[88–90]. These fusions are

targetable with several generations of EGFR TKIs and sustained clinical responses have been reported[88–90].

ALK.—Rearrangement of *ALK* is the second most common oncogenic driver alteration in LCINS and is found in up to 14% of these cancers[91], although this prevalence varies widely according to study design and population as well as between different age groups[7,78,92]. Overall, *ALK* rearrangements are found in ~5% of patients with NSCLC, with a roughly equal incidence in Asian and European populations[93]. Most patients with *ALK* rearrangements (70–80%) have never smoked[19], and up to 23% of *EGFR*-wild-type NSCLCs occurring in individuals <50 years of age with a history of never or light smoking harbour *ALK* rearrangements[94]. Similar to other molecular subtypes of LCINS, *ALK*-rearranged lung cancers are almost exclusively adenocarcinomas, although very rare cases of *ALK*-rearranged LSCC have been reported[95,96].

Other oncogenic fusions.—Novel gene fusions have been identified as oncogenic drivers in NSCLC using DNA-based and/or RNA-based NGS[80]. These include a variety of fusions involving *ROS1, RET, NTRK1–3, FGFR1, FGFR3* or *NRG1* as well as more recently identified *CLIP1–LTK* fusions[97,98]. *ROS1* and *RET* fusions each occur in approximately 1–4% of all LUADs, with the prevalence of other fusions estimated at <1%; detection sensitivities might be increased when using both DNA-based and RNA-based sequencing panels, particularly for *ROS1* and *RET* fusions[80]. Many of these fusions are enriched in LCINS as well as in younger patients and are targetable with various FDA-approved TKIs[97,99,100].

KRAS.—*KRAS* mutations comprise the largest molecularly defined subset of LUAD owing to the large percentage of smoking-related LUADs harbouring mutant *KRAS*. Activating point mutations in *KRAS* most commonly occur at codon 12 (G12C, G12D, G12V and G12A) and less commonly at codons 13, 10 or 61. *KRAS* mutations are found in only 5–15% of lung cancers occurring in white never-smoking patients[7,82,91,101], with the G12D variant being most common in this context (accounting for ~56% of *KRAS* mutations)[82]. By contrast, *KRAS* mutations are present in up to 47% of smoking-related LUADs[7], in which the G12C variant predominates (accounting for ~41% of these mutations)[82]. Indeed, transversions leading to the *KRAS* G12C, G12V, G12A and G12R variants are part of a mutational signature associated with tobacco carcinogens[82]. Nevertheless, smoking has the potential to cause transition mutations, albeit at a relatively lower frequency, thus accounting for the limited occurrence of mutations such as *KRAS* G12D in smoking-related LUADs. Furthermore, transversion mutations are also associated with non-tobacco exposures (for example, reactive oxygen species[102] and prior chemotherapy[103]), which might explain the occasional observation of *KRAS* G12C mutations in LCINS. A study comparing *KRAS* G12D-mutant versus non-G12D-mutant NSCLC revealed that *KRAS*^{G12D}-mutant tumours have lower PD-L1 expression, a lower tumour mutational burden (TMB), and lower intratumoural and total numbers of $CD8^{+}PD\text{-}1^{+}$ T cells. In keeping with these findings, *KRAS*^{G12D}-mutant disease was associated with a worse objective response rate (ORR; 15.8% versus 28.4%; $P = 0.03$), progression-free survival (HR 1.51, 95% CI 1.44–2.00; $P = 0.003$) and OS (HR 1.45, 95% CI 1.05–1.99; $P = 0.02$) when treated with anti-PD-

(L)1 antibody monotherapy[104]. Moreover, stratification of *KRAS*^{G12D}-mutant tumours by smoking status revealed that PD-L1 expression and TMB were markedly lower in those with a history of light or never smoking (<10 pack-years), and these patients (n = 12) had an ORR of 0% with single-agent PD-(L)1 blockade.

MET* alterations.—MET* alterations are present in a small subset of NSCLCs and consist of mutations resulting in *MET* exon 14 skipping (*METex14*; estimated prevalence of 1–4%)[80,105–108] and/or *MET* amplifications (prevalence of 1–6%, varying based on *MET* copy number)[109–111]. The percentage of patients with *METex14*-mutant NSCLC who have never smoked varies across studies (36–64%)[108,112]. One study found that *METex14* mutations are significantly more likely to be identified in those who have never smoked compared to *KRAS* mutations (P < 0.001) but are more likely to be associated with a smoking history than *EGFR* mutations (P = 0.03)[108]. Patients with *METex14*-mutant NSCLC tend to be older at diagnosis (median age >70 years)[108,112], whereas patients with *MET* amplifications are slightly younger (median age at diagnosis 60–64 years) and less often have a history of never smoking (7–34%)[112–114]. *MET* amplification also occurs as a mechanism of resistance to therapies targeting EGFR and ALK[115–117]. A high level of *MET* amplification (*MET*-to-*CEP7* ratio of ≥5 on fluorescence in situ hybridization (FISH) or a ≥5–10-fold increase in *MET* copy number detected via NGS) has been used to distinguish tumours that are more likely to be MET-driven, based on the absence of co-occurring oncogenic drivers and response to MET-directed TKIs (highest in tumours with *MET* copy number ≥10)[112,114,118]; high-level *MET* amplification is considered an emerging biomarker in the National Comprehensive Cancer Network (NCCN) Guidelines for NSCLC. Case reports have identified the presence of *MET* fusions (specifically *KIF5B–MET* and *STARD3NL–MET*) in LUADs from patients with a history of never or light smoking, which were targetable with crizotinib (a TKI with activity against MET)[119–121].

HER2.—Activating mutations in *ERBB2* (also known as *HER2*) occur in 1–3% of NSCLCs and up to 5% of LUADs[122–124], most commonly in patients who have never smoked and in women[124,125]. These mutations are typically small in-frame insertions in exon 20 (residues 770 to 783, most commonly the A775_G776insYVMA insertion or duplication) that result in constitutive HER2 kinase activity. Point mutations in the extracellular domain, transmembrane domain or kinase domain of *HER2* have also been identified (for example, G660D, R678Q, E693K and Q709L)[126,127]. Notably, germline *HER2*^{G660D} mutations have been identified in patients with familial lung cancer[127]. The relevance of *HER2* amplification and/or overexpression in NSCLC is less clear, and efforts to target HER2 in patients with NSCLC have been focused mostly on those harbouring activating *HER2* mutations, approximately 54–58% of which occur in patients who have never smoked[128,129].

Unknown drivers.—Large-scale genomic analyses of LCINS show that a small percentage of these tumours have no detectable oncogenic driver alterations (Fig. 2). In one of the largest aggregated studies of LUADs from never-smoking patients[7], samples deemed oncogene negative by WES had a lower mean tumour cellularity than those in which driver alterations were readily identified. Furthermore, among 13 tumours deemed oncogene negative based on standard-coverage WES, two were found to harbour *METex14* mutations

after additional deep WES (~400×)[7]. Exploratory WES and/or whole-genome sequencing (WGS) might uncover new variants in known driver oncogenes in regions not covered in current NGS panels, particularly in the case of fusions. Additionally, current variants of uncertain significance might be reclassified as oncogenic drivers (for example, the *EGFR* exon 18–25 kinase domain duplication[130] and kinase domain A955R[7] variants identified in 2021) in this population with a high pre-test probability of driver alterations. Moreover, ongoing genomic, epigenomic and proteomic analyses of LCINS are likely to elucidate new drivers and/or therapeutic targets.

Tumour mutational burden

LCINS generally have a markedly lower TMB (measured as non-synonymous mutations per megabase (mut/Mb)) in coding and non-coding regions compared to smoking-related lung cancers, with early studies suggesting as much as a tenfold difference[131] and a dose–response relationship between TMB and pack-years[132] (Table 1). Genomic profiling of >15,000 NSCLC samples has also revealed that *KRAS* and *BRAF* driver mutations, which are more commonly associated with a history of smoking, are associated with substantially higher TMB when compared to alterations in *EGFR, ALK* or *ROS1* (refs. 133,134). Responses to immune-checkpoint inhibitors (ICIs) in patients with NSCLC correlate with a high TMB as well as with a high number of transversions as part of a smoking-related mutational signature[135]. Indeed, the lack of ICI response associated with LCINS, and with NSCLCs harbouring alterations in *EGFR* or *ALK* more generally, is thought to partly reflect their lower TMB.

PD-L1 expression

PD-L1 expression is typically low or absent in LCINS[7,136] as well as in NSCLCs with non-*KRAS* oncogenic drivers[94,137]. Furthermore, PD-L1 positivity among *KRAS*-mutant lung cancers is lowest in patients who have never smoked, higher in those who formerly smoked and highest in those who currently smoke, with the intensity of staining positively correlating with pack-years of smoking history[136]. An exception is *METex14*-altered NSCLC, in which moderate to high levels of PD-L1 expression have been observed, although with a median TMB still substantially lower than that of unselected NSCLCs[138]. ICIs have been associated with low ORRs in patients with *METex14*-altered NSCLC (17–36% with ICI monotherapy[139]), and responses do not seem to correlate with PD-L1 expression or TMB[138]. *ALK*-rearranged and *ROS1*-rearranged NSCLCs are more frequently PD-L1 positive compared with *EGFR*-mutant NSCLCs[94,137,140–142] (70.1% and 72.7%, respectively, versus 50.3% in those with classical *EGFR* mutations)[142]; however, PD-L1 positivity in these tumours is thought to reflect differential intrinsic oncogene-driven activation of downstream signalling effectors that transcriptionally upregulate PD-L1 expression (such as STAT3 and HIF1α)[143,144] rather than reflecting true T cell-mediated immunogenicity through IFNγ signalling that correlates with a response to ICIs.

Genomic mutational signatures

Analysis of somatic alterations in lung cancers has enabled the identification of genomic mutational signatures that can emerge in tissues directly exposed to tobacco smoke. An analysis of WES or WGS data from 5,243 cancers of various types often associated

with smoking demonstrated an increased burden of somatic mutations and several distinct mutational signatures in tumours from patients with a history of tobacco smoking, with total base substitutions nearly fivefold higher in LUADs from such patients compared with LUADs from patients who have never smoked[40]. The smoking-associated single-base substitution signature 4, or simply ‘signature 4’, consists mainly of C>A transversions with lesser contributions from other base substitutions[40] and is very similar to the mutational signature that results from exposing cells to benzo[a]pyrene[145], a carcinogen found in tobacco smoke. This signature can also be found in cells derived from the non-malignant bronchial epithelium in individuals without cancer but with a former or current smoking status and is not present in non-malignant and tumour tissues from people who have never smoked[146]. Interestingly, most lung cancers occurring in patients with reported passive exposure to tobacco smoke also do not contain these signatures[7,78].

WES and WGS profiling of LCINS

Two large-scale genomic studies of LCINS were reported in 2021 (refs. 7,78). One study was a WGS analysis of 232 LCINS from patients of mostly European ancestry (97.4% European and 1.7% East Asian by inferred genetic ancestry) and described three different tumour subtypes according to somatic copy number alterations[78]. Approximately 60% of samples had alterations in *EGFR, KRAS, ALK, MET, HER2, RET* or *ROS1*. As expected, median TMB was sevenfold less than that of smoking-related lung cancers at 1.1 mut/Mb, and no tobacco smoking signatures were observed, even in cases with reported passive smoking exposure[78]. The second study was the previously discussed WES and RNA-seq analysis of 160 tumour and matched non-malignant tissue samples from never-smoking patients with LUAD, with a substantially higher percentage of East Asian patients (62% European and 25% East Asian by inferred genetic ancestry), and including 40 and 36 samples from The Cancer Genome Atlas (TCGA) and Clinical Proteomic Tumour Analysis Consortium cohorts, respectively[7]. As noted above, 78–92% of these LCINS harboured clinically actionable driver alterations, compared with 49.5% of smoking-related LUADs ($P < 0.001$). Only 6% of LCINS contained a smoking-related mutational signature potentially indicative of passive exposure to tobacco smoke, and the median TMB ranged from 1.25 to 2.93 mut/Mb across the internal and external (TCGA and Clinical Proteomic Tumour Analysis Consortium) cohorts. The immune landscape of these LUADs was examined using RNA-seq and consensus clustering of immune and stromal cell type markers. On the basis of PD-L1 and immune cell marker expression, three clusters were identified as relatively ‘immune cold’, ‘immune hot’ or intermediate tumours, with each cluster having a similar TMB and frequency of *EGFR* and *KRAS* mutations – suggesting the potential to identify subsets of LCINS that might be more likely to respond to immunotherapy.

Risk factors for LCINS

Genetic risk

Of the 20,000–40,000 LCINS diagnosed in the USA each year, second-hand smoke (SHS) and radon exposure are estimated to account for approximately 3,500 (ref. 13) and 2,900 cases[147], respectively. In the remainder, few consistent environmental associations can be found, posing the question of underlying genetic predisposition. Overall lung cancer

heritability has been estimated at 18%[148] and might be even greater in those who have not smoked. Several large-scale genome-wide association studies (GWAS) have investigated common polymorphisms associated with lung cancer risk, mainly for smoking-associated cancers. Collectively, >50 loci mediating a small to moderate amount of lung cancer risk have been identified[149]. Additionally, data on rare germline pathogenic variants, for example, in DNA damage repair or tumour-suppressor genes, are emerging from somatic mutation profiling studies (WES and/or WGS analyses) that use matched non-malignant tissues for comparison[150]. The implications of germline variants for lung cancer therapy and familial genetic screening are largely unexplored. Indeed, a study testing a panel of 76–88 cancer predisposition genes to evaluate the prevalence of therapeutically actionable germline variants in almost 12,000 patients across >50 different cancer types did not include lung cancer[151].

Family history of cancer can be used as a simplified surrogate for inherited susceptibility, particularly in the context of LCINS given that family members do not always share a history of tobacco smoking. This surrogacy is especially robust for rare, monogenic variants with large effect sizes, which are more likely to exhibit Mendelian patterns of inheritance within families than common variants with individually small effect sizes. A systematic review published in 2005 found that having a first-degree relative with lung cancer was associated with a twofold increased lung cancer risk; this was even greater when the first-degree relative was diagnosed at a young age and/or in individuals with multiple affected family members[152]. A subsequent study of epidemiological risk factors in people who had never smoked revealed that a family history of any cancer diagnosed before 50 years of age in a first-degree relative was a significant predictor of increased lung cancer risk (OR 1.87, 95% CI 1.13–3.10)[153]. Other proxies for genetic predisposition to lung cancer might include a lack of lifetime exposure to tobacco smoke and a young age at diagnosis, particularly for LCINS (which predominate lung cancer diagnoses among individuals <40 years of age)[16,18]. Nevertheless, such patients might not have a family history of lung cancer owing to rare pathogenic variants with incomplete penetrance or a polygenic risk architecture that obscures an inheritance pattern.

Insights from GWAS.—GWAS and candidate gene studies conducted over the past decade have identified common genetic variants, typically defined as single-nucleotide polymorphisms (SNPs) with a minor allele frequency of ≥1–5%, that are associated with lung cancer[149]. Common variant heritability is defined as the proportion of heritability that can be explained by common SNPs and has been estimated on an observed scale at 8.3% for lung cancer and 7.1% after removing genomic loci known to be associated with smoking behaviour[154]. Many studies using polygenic risk scores (PRS) to further estimate this attributable risk are under way. The GWAS have been focused mainly on smoking-related lung cancer (particularly a susceptibility locus at 15q25, corresponding to a cluster of nicotinic acetylcholine receptor subunit genes that mediate nicotine metabolism and smoking behaviour)[155–158], with several additional studies of LUAD in non-smoking Asian women. Reported susceptibility loci generally have a low to moderate effect size (OR 1–2) and, for many loci, suspected causal genes have been identified. To avoid spurious associations owing to population stratification (that is, systematic differences in

allele frequencies between subpopulations), GWAS are often restricted to individuals of a single ethnicity and/or ancestry. For this reason and because the landscape of NSCLC differs considerably between European and East Asian populations[159], most GWAS of lung cancer have considered these populations separately. A comprehensive review of all GWAS in lung cancer is beyond the scope of this article. Instead, key GWAS that have identified loci contributing to the risk of LCINS are summarized (Table 2).

One of the first GWAS to assess the genetic risk of lung cancer in individuals who have never smoked was conducted in Europeans, and the findings published in 2010 identified a single locus at 13q31.3 where variants resulting in lower transcription of *GPC5* were associated with increased susceptibility (OR 1.46, 95% CI 1.26–1.70; $P = 5.94 \times 10^{-6}$)[160]. *GPC5* encodes glypican 5, a proteoglycan with poorly understood roles in physiology and tumorigenesis. Interestingly, *GPC5* expression is reduced in LUAD but not in other histological subtypes of lung cancer compared with the surrounding non-malignant lung tissues[160]. The 5p15.33 locus containing *TERT* and *CLPTM1L* has been identified as a lung cancer susceptibility region in both smoking and non-smoking populations, including never-smoking women of East Asian descent[161–163] (Table 2). Although specific pathogenetic mechanisms have not been elaborated, this locus is associated with the risk of lung, bladder, prostate and cervical cancers in both European and Asian populations[162–164]. Results of a meta-analysis of GWAS performed in two independent cohorts to identify variants associated with OS in never-smoking European individuals with NSCLC were reported in 2013 (ref. 165). Out of the top 25 SNPs (combined $P < 1 \times 10^{-6}$), 6 variants showed a genotype–expression association upon expression quantitative trait loci analysis, none of which were within genes previously found to be associated with overall lung cancer risk in people who have not smoked nor within genes associated with OS in patients with smoking-related lung cancer[166–168].

GWAS of LCINS have been more extensive in patients of East Asian ancestry (Table 2), with risk variants at the aforementioned 5p15.33 locus recurrently identified in never-smoking women with LUAD[162,169,170]. Aside from this locus, the loci identified in never-smoking Asian women are generally distinct from those identified in European people with a history of smoking[160,163,171]. A LUAD susceptibility locus at 3q28 corresponding to *TP63* was first identified in Japanese and Korean populations (OR 1.31; $P = 7.26 \times 10^{-12}$), with a trend towards higher ORs in women but no clear differences by smoking behaviour[172], and was later confirmed specifically in never-smoking Asian women[163]. This locus was also subsequently associated with LUAD risk in European populations (OR 1.13; $P = 7.22 \times 10^{-10}$)[173]. A later study imputing data from four prior GWAS of lung cancer in never-smoking Asian women using the 1000 Genomes Project identified three new risk loci with small effect sizes at 6p21.1, 9p21.3 and 12q13.13, which map near *FOXP4, CDKN2B* and *ACVR1B*, respectively[174] (Table 2). Subsequent studies in never-smoking Korean populations have identified additional LCINS susceptibility regions on chromosomes 2 and 18[171,175] (Table 2).

Most recently, a large, two-stage GWAS of LUAD occurring in individuals of East Asian ancestry identified 12 novel susceptibility variants[159] and identified novel alveolar lineage-specific candidate genes, including *FADS1* and *ELF5*, via expression quantitative trait

loci colocalization analyses. A multi-ancestry meta-analysis performed as part of the same study revealed four additional novel risk loci shared among East Asian and European individuals (Table 2), although the majority of associations identified in the East Asian cohorts did not extend to the European population. Historically, few studies have identified gene–environment interactions in lung cancer risk[176]. However, a PRS generated from the top 25 independent susceptibility variants that achieved genome-wide significance in the East Asian population stratified individuals in the highest risk quintile from those in the middle quintile (corresponding to average risk in the general population) to a greater extent in the non-smoking versus smoking population (OR 2.07 versus 1.80; $P_{\text{Interaction}}$ = 0.0058)[159].

Taken together, the results from GWAS of LCINS are largely non-overlapping and have not converged on a set of robust associations. An analysis by the Transdisciplinary Research In Cancer of the Lung (TRICL) consortium using a custom SNP array restricted to rare variants in known cancer-associated genes identified a large effect association between germline *ATM* L2307F mutations and LUAD (OR 2.93–8.82 across discovery and replication cohorts)[177]. This effect seemed to be independent of smoking status, although never-smoking women carrying the L2307F variant were approximately four to seven times more likely to develop LUAD than non-carriers. Notably, this variant is much more prevalent in the Ashkenazi Jewish population (~4%) and might constitute a founder mutation. Variant-associated clinicopathological variables reaching high levels of statistical significance included never-smoking status and female sex but also adenocarcinoma histology and the presence of a somatic *EGFR* mutation[177]. Interestingly, never-smoking patients with lung cancers harbouring somatic *EGFR* mutations are more likely than those with *EGFR*-wild-type tumours to have a family history of lung cancer[178,179]. Moreover, a lung cancer genomics and ancestry analysis of admixed Latin American populations demonstrated that the frequency of somatic *EGFR* mutations varies by ethnicity, suggesting a germline component to *EGFR* mutation status[180].

Polygenic risk scores.—PRS integrate the risk associated with GWAS-identified, disease-associated common SNPs present in the genome of an individual into weighted averages to produce a ‘personalized genetic susceptibility profile’ as a single measure of risk. Using data generated from previous GWAS conducted predominantly in people with a history of smoking, researchers developed PRS specific for 16 different cancer types; the investigators then compared the ability of the PRS versus self-reported family history of cancer in first-degree relatives to predict the risk of cancer within 5 years among 413,870 individuals included in the UK Biobank (with 22,755 incident cancer cases)[181]. Interestingly, lung cancer was unique in that family history was a significantly better predictor of risk than PRS, such that individuals with a positive family history and a low PRS had a higher 5-year risk of lung cancer than those with a high PRS and negative family history (0.54% versus 0.46%)[181]. This trend was not observed for several other common cancers, including prostate, breast and colorectal cancers. Assuming that affected relatives from different families did not share common exposures, this finding indicates that lung cancer heritability might be largely attributable to rare, high-effect alleles that mediate familial risk, although a possible alternative explanation is that a positive family

history better predicted the risk in individuals who had not smoked given that the PRS was generated from GWAS of predominantly smoking-related NSCLCs.

Another lung cancer-specific PRS was generated by combining genetic and epidemiological data from approximately 13,000 patients and 10,000 control individuals and subsequently validated in almost 336,000 individuals included in the UK Biobank[182]. This PRS was generated based on a population in which >90% of patients had a history of smoking; therefore, a de novo model to predict the risk of LCINS was derived based on age, sex, body mass index, family and personal history of cancer, impaired lung function, and exposure to ambient air pollution and SHS, in addition to PRS[182]. Interestingly, including environmental exposures did not improve the predictive performance of the model for LCINS[182], which is in contrast to the previously mentioned data from East Asian populations showing an interaction of PRS with smoking status[159], probably because smoking is a stronger risk factor.

Ultimately, family history and PRS are not mutually exclusive but rather complementary factors that can provide different insights into the cancer risk of an individual. Indeed, combining family history and PRS has been shown to enhance risk assessment for breast and prostate cancers[183,184], although a PRS for these malignancies has not yet been integrated into clinical practice. Whether PRS will have meaningful utility in predicting lung cancer risk remains unclear, and further efforts in this area will probably need to distinguish between smoking-related versus non-smoking-related lung cancers.

Insights from WES and WGS.—Susceptibility loci identified in GWAS account for only a small portion of the variation in lung cancer incidence, mainly because GWAS typically detect common variants with small to moderate effect sizes. Studies at the exome and genome levels are therefore needed to identify rare, large-effect/high-risk germline variants; only a handful of germline analyses in lung cancer have been conducted at these levels, either using data gleaned from matched non-malignant tissues in somatic tumour-profiling studies or as dedicated germline-directed efforts. The largest widely available datasets are derived from TCGA[185] (containing WES data from ~580 LUADs and paired non-malignant tissues and WGS data from ~100 tumours) and the Hartwig Medical Foundation[186,187]. Additional datasets come from the Pan-Cancer Analysis of Whole Genomes (PCAWG) project[188] as well as a WES study of LUAD in patients of East Asian ancestry[189]. In the Hartwig Medical Foundation cohort, which included 178 patients with lung cancer[186], various nonsense, frameshift or splice site-altering germline variants were found in *CHEK2* and Fanconi anaemia complementation group (FANC) genes (*FANCI, FANCL, FANCM*), involved in DNA repair, as well as *DOCK8* and *GJB2* (encoding dedicator of cytokinesis protein 8 and gap junction β2 protein, respectively). A germline WES study focused on SCLC or extrapulmonary small-cell carcinoma identified 42 deleterious germline variants across 35 cancer predisposition genes in 38 (44%) of 87 patients, although 90% had a current or former smoking status[190].

WES and/or WGS studies had not distinguished between smoking and non-smoking individuals until 2021, when results emerged from the two formerly discussed somatic alteration profiling studies of never-smoking LUAD, which included data from matched

non-malignant tissue analyses[7,78]. In the WGS study[78], 8 of 232 patients carried pathogenic germline variants (PGVs) in *CYP21A2*, which encodes the 21-hydroxylase enzyme involved in the synthesis of cortisol and aldosterone, 6 patients carried the same PGV in *GLUD2*, which encodes the mitochondrial enzyme glutamate dehydrogenase 2, and 5 patients had PGVs in the *AR* gene (encoding the androgen receptor); PGVs in *BRCA1, ATM* and *RAD51* were each found in 2 or 3 patients. Interestingly, both *CYP21A2* and *AR* are involved in hormone production and signalling, and might thus contribute to sex differences in the incidence of LCINS. In the WES study[7], rare pathogenic or likely pathogenic (P/LP) mutations in known cancer predisposition genes were identified in patients who had never smoked; although the prevalence of P/LP mutations was similar to that in those who had smoked (6.9% and 6.4%, respectively), variants in *BRCA1, BRCA2, FANCG, FANCM, HMBS, MSH6, NF1,POLD1, TMEM127* and *WRN* were exclusive to never-smoking individuals. Using a cancer-free control cohort derived from the Genome Aggregation Database (gnomAD), the never-smoking LUAD group was enriched for P/LP variants in *FANCG* (encoding a component of the Fanconi anaemia DNA repair complex) and *TMEM127* (encoding a negative regulator of mTOR signalling).

Larger sample sizes along with functional validation will be needed to further implicate these germline variants in lung cancer pathogenesis, although these early studies in individuals who have never smoked have highlighted the presence of pathogenic alterations with large effect sizes in DNA repair-related genes. This finding is underscored by data from a broader study of common diseases showing that patients with a low common variant PRS are more likely to carry rare disease-specific pathogenic variants[191], suggesting that these individuals could be prioritized for rare variant screening.

Lastly, in a study using WES data from participants in the UK Biobank and Mass General Brigham Biobank, the presence of clonal haematopoiesis was found to be associated with increased risk of lung cancer (meta-analysed OR 1.35, 95% CI 1.08–1.68)[192], specifically for LUAD (OR 1.68, 95% CI 1.23–2.29) and LSCC (OR 1.59, 95% CI 1.51–1.68) but not for SCLC. Clonal haematopoiesis was also associated with a 36% increase in lung cancer risk among the UK Biobank participants after adjusting for major risk factors, including pack-years of smoking, age at sequencing, family history of lung cancer and lung cancer PRS[192]. Whether clonal haematopoiesis is a surrogate of currently unknown shared risk factors, including inherited genetic risk (for example, mediated by rare variants), or has a more causal role in lung cancer remains unclear.

Germline *EGFR* mutations in familial lung cancer.—Germline *EGFR* mutations have been identified in familial lung cancers[193]. Most common is the T790M mutation, which, in its somatic form, can be present at diagnosis or develop as a mechanism of resistance to earlier-generation EGFR TKIs. The germline $EGFR^{T790M}$ mutation was identified in 2005 among a family of European descent with several members across multiple generations developing LUAD[193]. Germline $EGFR^{T790M}$ has since been found in multiple unrelated kindreds, predominantly comprising white individuals in the USA, Europe and Australia, more frequently in never-smoking women, and in association with multiple primary lung lesions (either nodules or invasive adenocarcinomas)[193–196]. A cluster of families has been identified in the southeastern USA, suggesting a possible founder

effect[197]. Notably, germline *EGFR*^{T790M} has not been reported in patients of East Asian ethnicity with lung cancer despite the high prevalence of somatic *EGFR* mutations in this population. Germline *EGFR*^{T790M} mutations have been estimated to occur in 0.5–1.0% of patients with NSCLC[195,198] and in roughly 1 in 100,000 individuals in the general population[194] (allele frequency of 9.9×10^{-6} in the gnomAD v4.0 database)[199]. Additional studies with larger sample sizes are needed to determine more precise frequencies of germline *EGFR*^{T790M} mutations in patients with lung cancer as well as the magnitude of their effect on lung cancer risk.

Virtually all lung cancers that develop in the context of a germline *EGFR* mutation harbour a secondary somatic activating mutation in *EGFR* in cis[193], most commonly L858R[197,200]. *EGFR*^{T790M} carriers without known lung cancer are often found to have multiple groundglass nodules on CT imaging, suggestive of premalignant lesions that can develop into invasive adenocarcinoma over time[194], and are likely to benefit from surveillance CT-based screening. *EGFR*^{T790M} carriers do not seem to have an increased incidence of any other cancer type; the mechanism underlying LUAD specificity is unknown. Less common germline *EGFR* mutations include R776G/H[201,202] and V769M in exon 20 (ref. 203) and V834L and V843I in exon 21, the latter identified specifically in Asian and Surinamese families[204–206]. Even rarer is the *EGFR* R831H germline variant reported in Chinese patients with NSCLC[207,208], which was also described as co-segregating with prostate cancers harbouring somatic biallelic inactivation of *CDK12* in two brothers within one family; prostate cancer cells derived from these patients were responsive to the EGFR TKI afatinib in vitro[209]. To our knowledge, *EGFR*^{R831H} is the only germline *EGFR* mutation associated with a cancer type outside of the lung, although genotype–phenotype relationships among various germline *EGFR* mutations have not been extensively studied. Additional genetic or environmental modifiers might affect the lung cancer risk associated with germline *EGFR* mutations and account for phenotypic differences between individuals within families, despite carrying the same mutation.

Non-*EGFR* germline mutations in familial lung cancer.—Germline mutations in familial lung cancer pedigrees have also been found in *HER2* (refs. 210-212), *BRCA2, CHEK2* (ref. 173), *MET*[213] and *YAP1* (ref. 214), predominantly in never-smoking patients with LUAD and more commonly in female patients. The germline G660D mutation in the transmembrane domain of *HER2* was initially reported in a Japanese family, identified in a female proband with a 1.2 pack-year smoking history and multifocal NSCLC[210]. Following lobectomy, pathology demonstrated that this woman had innumerable pre-invasive lesions; similar lesions were seen bilaterally on imaging in her 30-year-old daughter, also a *HER2*^{G660D} carrier[212]. No additional somatic alterations were identified (including *HER2* and *EGFR*), and the proband was treated with second-line afatinib following disease progression on chemotherapy, with a partial response in the lung and stable disease for ≥16 months in the bone[211]. Additionally, a candidate gene study using WGS in a never-smoking Taiwanese family with high frequency of LUAD identified a germline variant (R331W) in the transactivation domain of *YAP1* (ref. 214), a transcriptional regulator in the Hippo signalling pathway that has been implicated in resistance of *EGFR*-mutant NSCLC to EGFR TKIs[215,216]. In a validation cohort derived from the Genetic Epidemiology Study of Lung

Adenocarcinoma in Taiwan, the *YAP1*^{R331W} allele frequency was 1.1% in patients with LUAD versus 0.18% in individuals without cancer, translating into an OR of 5.9 after adjusting for age, sex and smoking status[214]. All chest CT-screened *YAP1*^{R331W} carriers had LUAD or groundglass lesions (40% and 60%, respectively)[214]. These studies support the existence of rare, highly penetrant PGVs that contribute to a subset of LCINS.

Hereditary cancer predisposition syndromes.—LUAD is a principal malignancy associated with several multi-organ cancer predisposition syndromes resulting from germline mutation of tumour-suppressor genes (for example, *TP53, PTEN* or *LKB1*)[217]. Several case reports have demonstrated oncogene-driven NSCLC in patients with Li–Fraumeni syndrome[218–221]. In one study, 21 (91%) of 23 NSCLC tumours in patients with Li–Fraumeni syndrome harboured an oncogenic alteration, 20 (87%) of which were *EGFR* mutations, most commonly exon 19 deletions[220]. *EGFR*-mutant LUAD has also been described in Cowden syndrome, caused by germline *PTEN* mutations, in case reports of younger patients with a history of light or never smoking[222]. An increased risk of lung cancer has been reported in survivors of hereditary retinoblastoma with germline *RB1* mutations, with lung cancer diagnosis tending to occur before 40 years of age[223], and there are case reports of lung cancers associated with Bloom[224], Werner[225] and Birt–Hogg–Dube syndromes[217].

Environmental risk factors

Various environmental exposures have been implicated or hypothesized to contribute to the risk of LCINS (Table 3). An exhaustive discussion of these risk factors is beyond the scope of this Review; here, we focus on key exposures with established associations and/or those with contemporary evidence of an effect on lung cancer risk.

Radon.—Radon has been identified as the second-leading environmental cause of lung cancer (after tobacco smoking) and is estimated to contribute to ~21,000 lung cancer-related deaths annually in the USA, with roughly 2,900 of these deaths occurring in individuals who have never smoked[147,226,227]. The increased lung cancer incidence associated with radon was first noted in uranium miners in the 1980s[228–230], and numerous large, international epidemiological case–control studies have also demonstrated an association between prolonged residential radon exposure and lung cancer in the general public[231–239]. These and additional studies led the US Environmental Protection Agency (EPA) to classify radon as a carcinogen owing to its causal association with lung cancer, and both the EPA and the National Radon Safety Board advocate radon screening and mitigation in homes across the USA[240,241].

Radon exposure more than additively increases the lung cancer risk conferred by smoking[234,242]. In comparison with non-smoking individuals, lung cancer risk associated with radon exposure is eightfold to ninefold greater in individuals who also smoke, and >85% of radon-associated lung cancers occur in those who formerly smoked or currently smoke[230,243], although the risk is still substantial in non-smoking groups[244]. Subsequent studies and meta-analyses have shown the strongest histological association of residential radon exposure with SCLC, followed by LUAD[245–247]. A population-based, case–control

study performed among ~530 women with LCINS did not find an association between lung cancer and domestic levels of radon exposure, potentially owing to a relatively low level of exposure or differences in underlying genetic susceptibility. Interestingly, a meta-analysis has revealed a higher adjusted excess relative risk of lung cancer from residential radon exposure for men than for women among those who had never smoked (0.46 versus 0.09; $P = 0.027$)[248].

Secondhand smoke.—SHS has long been studied as a potential causative factor in LCINS. SHS exposure is estimated to increase lung cancer risk by 20–25% in individuals who do not smoke and, in 2023, a projected 3,560 lung cancer-related deaths among non-smoking individuals in the USA were attributable to SHS[1,13]. In addition to the duration and intensity of exposure, genetic modifiers influencing carcinogen metabolism, DNA repair and inflammation all probably affect the lung cancer risk conferred by SHS[249–252].

Many epidemiological studies performed in the 1990s to early 2000s established SHS as a risk factor for LCINS[153,253–256], although the effect sizes are moderate. Most of these studies have compared individuals who have a spouse who smokes with those who do not. In a meta-analysis of 37 such studies ($n = 4,600$), the pooled relative risk of lung cancer in women who were exposed to SHS versus those who were not was 1.24 (95% CI 1.13–1.36; $P < 0.001$)[253]. A subsequent and much smaller case–control study including 280 patients with LCINS found a larger effect (OR 2.08, 95% CI 1.25–3.43 across both sexes) but lower than that associated with exposure to environmental dust (OR 2.43, 95% CI 1.53–3.88)[153]. Interestingly, a large prospective cohort study involving >75,000 women revealed a 13-fold higher incidence of lung cancer in individuals who currently smoke (HR 13.44, 95% CI 10.80–16.75) and fourfold higher incidence in those who formerly smoked (HR 4.20, 95% CI 3.48–5.08) compared with those who had never smoked, but no increase was observed among never-smoking women with passive smoke exposure (HR 0.88, 95% CI 0.52–1.49)[257]. Despite the limited number of lung cancers in never-smoking women with SHS exposure, a borderline significant trend towards an increased risk of lung cancer was observed in those who cohabitated for ≥30 years with someone who smoked (HR 1.61, 95% CI 1.00–2.58)[257].

The molecular characteristics of SHS-associated lung cancers are similar to those of tumours in never-smoking patients, with no overall difference in rates of *EGFR, ALK, KRAS, HER2, BRAF* and *PIK3CA* alterations[258]. Although tobacco carcinogen metabolites have been found in the urine and blood of never-smoking individuals exposed to SHS[253], large-scale genomic studies of LCINS have shown that reported SHS exposure often does not correlate with smoking-related somatic mutational signatures[7,78]. Indeed, the small group in which such signatures were detected might consist of individuals with the highest SHS exposure and/or underlying genetic susceptibility to carcinogenesis. The WHO International Agency for Research in Cancer (IARC)[259] and US National Institutes of Health[260] have designated SHS as a human carcinogen, although SHS is generally accepted to confer only a modest risk of cancer and is not considered the sole causative factor for the majority of LCINS. Nonetheless, household exposure is probably more relevant than public exposure, and the continued declines in smoking rates as well as health regulations outlawing smoking in indoor public spaces will further mitigate the effects of SHS.

Air pollution.—Air quality can be measured by quantifying the amounts of ozone, particulate matter and chemical pollutants in ambient air. Particle pollution is a combination of small liquid and solid particles that can comprise dust, metals, soil, acids and organic chemicals. These small, inhaled particles emitted from vehicle exhaust, forest fires, coal-fired power plants and other industrial sources are thought to pass through the central airways and lodge in the more peripheral airways where LUADs typically form. The association between outdoor air pollution and lung cancer risk has been reported in several studies[261–267], and both air pollution and particulate matter have been officially classified as group 1 carcinogens by the IARC[265,268]. Particulate matter with a diameter of ≤2.5 μm ($PM_{2.5}$) can reach the alveoli and has been associated with heart disease and lung cancer[263,266,267,269]. According to the IARC, the largest and most important studies consist of combined analyses spanning 17 cohorts from 9 countries in Europe[263] and a multi-cohort study among large cities in the USA[266], reporting HRs of 1.18 and 1.55 per 5 μg/m^3 of $PM_{2.5}$ exposure for lung cancer and LUAD, respectively. Additionally, a large study in those who had never smoked showed a 15–27% increase in lung cancer mortality per 10 μg/m^3 increase in $PM_{2.5}$ concentrations[267]. In 2016, the IARC estimated that ~6% of outdoor air pollution-related premature deaths were attributable to lung cancer[268]. Unsurprisingly, risk is proportional to the extent of exposure[270] and is greater than additive when combined with cigarette smoking (risk of lung cancer mortality 2.2 times greater than additive for joint exposure)[271], although evidence indicates an increased risk even after accounting for smoking[263,272] as well as when restricting the analysis to those who have never smoked[267]. The updated 2021 WHO global air quality guidelines[273] recommend annual mean $PM_{2.5}$ concentrations of ≤5 μg/m^3, while the EPA primary standard[274] is ≤12 μg/m^3, with a proposal in January 2023 to revise this standard to 9.0–10.0 μg/m^3 (ref. 275). Modelled annual mean $PM_{2.5}$ concentrations for the USA[276] and globally[277] show the highest levels in portions of the Midwest, Southeast and California within the USA, and in northern Africa, India, China and Middle Eastern countries internationally (Fig. 3).

As with other environmental exposures, the lung cancer risk conferred by air pollution is probably influenced by underlying genetic susceptibility[265,278] (Fig. 4a). In 2021, a study analysed SNP data from >450,000 individuals included in the UK Biobank combined with estimated particulate matter exposure[265]. After controlling for confounders, such as obesity and smoking, the investigators generated a PRS to model genetic risk and found an additive interaction between genetic susceptibility and air pollution, such that individuals with high genetic risk and high levels of exposure to air pollution were at greatest risk of developing lung cancer ($PM_{2.5}$: HR 1.71, 95% CI 1.45–2.02) relative to those with low genetic risk and low air pollution exposure.

More recently, another study used UK Biobank data to examine exposure to $PM_{2.5}$ in >400,000 individuals residing in the UK[279]. Increasing levels of $PM_{2.5}$ exposure correlated with increased risk of lung cancer (HR 1.08; 95% CI 1.04–1.12); nominally significant (P < 0.05 and false discovery rate > 0.05) associations were also reported for mesothelioma (HR 1.11, 95% CI 1.00–1.24) and lip and oropharyngeal cancers (HR 1.10, 95% CI 1.01–1.19). Analyses of the interaction between $PM_{2.5}$ exposure and ever-smoking status indicated that current or previous smoking and exposure to high levels of $PM_{2.5}$ might

act in combination to increase lung cancer risk ($P = 0.049$). Interestingly, $PM_{2.5}$ levels correlated with the incidence of *EGFR*-mutant lung cancer in England as well as in South Korea and Taiwan, with the relative rates per 100,000 individuals increasing by 0.63 ($P = 0.0028$), 0.71 ($P = 0.0091$) and 1.82 ($P = 4.01 \times 10^{-6}$), respectively, with each additional 1 μg/m^3 $PM_{2.5}$ increment. Interestingly, DNA sequencing of non-malignant lung tissue revealed *EGFR* and *KRAS* mutations in 18% (54 out of 295) and 53% (43 out of 81) of samples, respectively, leading to the hypothesis that these mutations accumulate as part of the ageing process and that $PM_{2.5}$ promotes subsequent tumour formation in the 'at-risk epithelium' harbouring these driver mutations[279]. Further studies are necessary to elucidate the degree of lung cancer risk conferred by $PM_{2.5}$, particularly with regards to the amount and duration of exposure, as well as the direct mechanistic link between $PM_{2.5}$ and *EGFR* and *KRAS* mutation and/or tumorigenesis driven by these alterations. Importantly, inequities in exposure to air pollution disproportionately affect lower socioeconomic status groups and non-white populations[280] as well as those with less education or who live closer to major sources of pollution, necessitating a global effort to improve air quality for the most vulnerable populations.

Occupational carcinogens.—In an extraction of data from the IARC monographs (spanning years 1971–2017), 20 different agents and their related compounds were found to be causally associated with lung cancer[281] (Table 3). Several of these exposures (for example, silica, diesel exhaust and welding fumes) increase lung cancer risk independent of smoking status and co-exposures[282–284]. A large pooled analysis assessing the risk of lung cancer in men exposed to diesel exhaust fumes (with 16,901 cases and 20,965 controls) found an exposure–response relationship regardless of smoking history (OR 1.41, 95% CI 1.30–1.52 in never-smoking individuals at the highest exposure level), particularly for LSCC and SCLC (OR 1.38 for both cancer types at any exposure level, 95% CI 0.98–1.94 and 0.81–2.36, respectively)[283]. Similar exposure–response relationships were demonstrated for all histological subtypes of lung cancer using the same dataset to assess the risk associated with respirable crystalline silica[282].

Exposure to asbestos is definitively associated with a high risk of both bronchogenic carcinoma and pleural mesothelioma[285,286], with the risk being several-fold higher for lung cancer than mesothelioma. Nevertheless, approximately 80% of patients with pleural mesothelioma report asbestos exposure[287], and 15–20% of all asbestos-related deaths in the USA result from mesothelioma[288]. Although these proportions are decreasing owing to asbestos abatement laws effected in the latter half of the twentieth century, they are likely to remain considerable for at least a decade owing to a long latency period to lung cancer development (15–35 years). Individuals employed in mining, construction, shipbuilding and firefighting as well as veterans exposed to military asbestos products continue to constitute the groups at highest risk. The risk of lung cancer is greatly multiplied when asbestos exposure is combined with cigarette smoking[286,289–292] (OR 8.70 versus 1.70 in those exposed to asbestos who never smoked)[292]. In men with LUAD, an association has been found between occupational asbestos exposure and an increased prevalence of *KRAS* codon 12 mutations, independent of smoking status and age (adjusted OR 6.9, 95% CI 1.7–28.6)[293]. In addition to occupational exposure, lung cancer risk might be higher

in individuals who live near environmental sources of asbestos (OR 1.48, 95% CI 1.18–1.86)[294].

Electronic cigarettes and vaping.—Whether the use of electronic cigarettes (e-cigarettes) and similar devices is associated with an increased incidence or risk of lung cancer remains unclear owing to their relatively recent development and the tendency for users to also smoke tobacco. Nicotine exposure in the absence of tobacco smoking is not thought to increase cancer risk based on studies involving users of nicotine replacement therapy[295,296], although these studies have had relatively short surveillance times (for example, 5–7 years). In fact, when used as tools for smoking cessation, nicotine replacement therapy has been correlated with a decrease in lung cancer risk and mortality[297–300]. Several thousand cases of severe vaping-related lung injury were reported in 2019 (ref. 301), thereafter known as e-cigarette or vaping product use-associated lung injury, largely owing to vitamin E acetate contamination of e-cigarette cartridges with either manufacturer-derived or illicit substances. However, the carcinogenic potential of e-cigarette vapours is less clear, and their acute and chronic effects probably depend on the composition of the liquid being aerosolized, the specific device used and user habits[302–304]. When heated, common nicotine solvents can yield byproducts, such as propylene oxide and acrolein, that are carcinogenic[305–307]. Depending on the aerosol, e-cigarette vapour can contain ultrafine particles (<0.3 μm in diameter) capable of reaching pulmonary alveolar regions, the distribution of which is also dependent on liquid solvent content (for example, vegetable glycerin-to-propylene glycol ratio) and inhalation practices[303,308,309]. Although similar in size to those found in tobacco and diesel engine smoke, the carcinogenic potential of vaping particles is unknown. Ultimately, long-term follow-up studies are needed to determine any association between e-cigarette use and lung cancer.

Household use of solid fuels and high-temperature frying.—Fumes and particulate matter generated from burning cooking oils and solid fuels used for heating (consisting of ‘smoky’ or bituminous coal and ‘biomass’ such as wood, charcoal and crop residue) contribute to indoor air pollution in homes across the world, particularly in developing nations and parts of Africa and Southeast Asia. These emissions contain known carcinogen substances, mainly polyaromatic hydrocarbons and aldehydes as well as particulate matter with a diameter of ≤0.25 μm, that have been classified as group 1 (carcinogenic) or group 2 (likely carcinogenic) by the IARC[310] based on numerous studies worldwide. Traditional cooking in many Asian countries involves heating cooking oils to very high temperatures during the process of frying, which has historically exposed women to the resulting carcinogens to a greater extent than men. A dose–response relationship has been observed between reported exposure to cooking oil fumes and lung cancer risk, which is generally higher with deep frying versus stir-frying and in homes with poor ventilation[311–313]. With respect to indoor burning of coal, a large retrospective cohort study among smoky coal users in China (n = 27,310) found that the absolute risk of death from lung cancer before 70 years of age was 18% and 20% for men and women, respectively, compared with <0.5% for both sexes among smokeless coal users (n = 9,962), regardless of tobacco smoking status[314]. The lung cancer risk associated with indoor burning of wood and other biomass is similar to that attributed to coal smoke, with ORs of <2; the risk is

greater in women than in men[315–317], which might reflect a greater amount of time spent in the household by women and might therefore be associated with the social construct of female gender rather than being biologically related to female sex. Household pollutants are predominantly associated with LUAD, although cases of LSCC and SCLC have been reported. Whether an underlying genetic susceptibility contributes to the lung cancer risk associated with indoor pollutants remains unclear.

Germline–somatic–environment interactions

Cancers arise in the context of a complex interplay between germline and somatic genomes and the environment (Fig. 4a). With regard to lung cancer, the architecture of germline risk includes many small-effect common variants and larger-effect rare and ultra-rare variants. Established rare risk variants include loss-of-function mutations in tumour-suppressor genes as well as gain-of-function alterations in oncogenes, the latter of which underlie familial lung cancer syndromes associated with germline mutations in *EGFR* and *HER2*. Interactions between inherited genetic variants and the acquisition of somatic alterations as well as environmental exposures can affect the risk and management of LCINS (Fig. 4), underscoring the importance of studies evaluating matched tumour and non-malignant tissue samples. An example of such an interaction comes from the previously discussed study in which germline ATM^{L2307F} mutations were found to be associated with LUAD arising in individuals with a history of light versus heavy smoking, later age of onset, and broad and local somatic features (that is, *EGFR* mutation and biallelic *ATM* inactivation, respectively)[177].

Potential mechanisms for this interaction include (1) cooperation between germline and somatic variants in different pathways to promote a clonal advantage[318], (2) germline variants acting downstream of somatic variants to modulate clonal advantage (and vice versa), (3) germline variants promoting the formation of larger-scale somatic events such as chromosomal abnormalities[177], and (4) germline variants (for example, in DNA repair pathways) contributing to clonal advantage, agnostic to the nature of the somatic mutation driving the clone. Treatments for lung cancer typically target somatic alterations irrespective of germline genetic background, although a study in patients with SCLC demonstrated that PGVs in DNA repair genes can influence recurrence-free survival and response to agents targeting defective DNA repair[190]. Considering ICI treatment and toxicity, a germline PRS enriched for variants regulating gene expression in macrophages and dendritic cells has been shown to predict the nature of the tumour immune microenvironment and ICI response[318]. Additionally, a germline PRS for hypothyroidism is predictive of thyroid-specific immune-related adverse events in patients with NSCLC[319]. Moreover, a cross-cancer GWAS among patients receiving ICIs identified three common variants that are associated with all-grade immune-related adverse events, the most consistently replicated of which was an intronic variant in *IL7* that is predictive of increased lymphocyte stability after ICI initiation as well as improved OS[320]. Thus, underlying germline variation can affect both tumour evolution and the development of targetable somatic alterations, and consequently influence treatment response and clinical outcomes.

Diagnostic and management considerations

Given the high likelihood of targetable somatic alterations, several diagnostic and management principles can be applied to LCINS (Fig. 5). The NCCN Guidelines for NSCLC[321] recommend testing for mutations or fusions involving the following 11 oncogenes: *EGFR, KRAS, ALK, ROS1, RET, HER2, N7RK1–3, BRAF* and *MET* (exon 14 skipping), with high-level *MET* amplification as an emerging target. Testing methods vary, although panel-based NGS is preferable to maximize target coverage. Blood-based NGS might not detect driver alterations owing to insufficient shedding of tumour DNA; therefore, samples cannot be deemed oncogene negative based on liquid biopsy results alone. Most fusions (for example, those involving *ALK, ROS1* or *RET*) are detectable with break-apart FISH assays or hybrid capture-based NGS, and DNA-based NGS has been used to identify novel fusion partners not detectable with FISH and reverse transcription PCR[80]. However, genomic breakpoints for rarer fusions (for example, involving *NTRK1–3* or *NRG1* as well as some *ROS1* fusions) can occur within long intronic sequences that are not adequately covered in targeted DNA-based panels. For this reason, RNA-based NGS has been used, and can also enable the identification of fusions when low tumour purity limits DNA-based detection owing to the high expression of fusion oncogenes. Broader sequencing efforts, such as WES, can reveal therapeutic targets, particularly in the case of novel fusions or other genomic alterations in regions with low coverage in standard NGS panels.

The management of LCINS is largely driven by genomic findings as outlined in NCCN guidelines for NSCLC[321]. Discussion of genotype-directed therapy is beyond the scope of this Review but, for patients with advanced-stage disease, targeted therapy is generally preferable when available[321]. Newer strategies involving TKI treatment to the point of maximal response followed by local consolidative treatment are under investigation[322–325] as are upfront combinations of targeted agents with chemotherapy in patients with advanced-stage disease[326]. For patients with central nervous system metastases at diagnosis but without severe mass effects and in whom a targetable alteration is found for which a central nervous system-penetrant TKI is available, potential therapeutic strategies include TKI treatment prior to radiotherapy or surgical resection of brain lesions given the high intracranial efficacy of these drugs in clinical trials; however, comparisons with upfront radiotherapy and/or surgery have not yet been made. Ongoing or completed clinical trials have also incorporated targeted therapies in the neoadjuvant and adjuvant settings[327–330]. Indeed, adjuvant osimertinib is now approved for patients with completely resected stage IB–IIIA *EGFR*-mutant NSCLC, with a final analysis of the phase III ADAURA trial showing 5-year OS of 88% with osimertinib versus 78% with placebo (HR 0.49, 95% CI 0.33–0.73)[328,331].

In individuals with an elevated germline risk of cancer, screening has an important role in disease prevention. Low-dose CT (LDCT) screening has been shown to reduce lung cancer mortality[332,333] but is only approved for individuals ≥50 years of age with a current or recent heavy smoking status. Future efforts in the LCINS space include identifying a population with elevated germline and/or exposure-mediated risk to prioritize for LDCT screening (for example, individuals carrying large-effect rare variants associated with familial *EGFR*-mutant lung cancer), with studies already under way (such as NCT05587439

and NCT05265429). These individuals might benefit from germline genetic testing and carriers of pathogenic variants might also benefit from LDCT screening as part of future changes to clinical care.

Conclusions

LCINS is an evolving and complex disease with several risk factors and open questions. With smoking rates declining, LCINS might eventually predominate lung cancer diagnoses. Investigations with specific attention to smoking history are therefore paramount both for determining the global and national trends in LCINS epidemiology, and establishing registries with detailed exposure histories. Advances have been made in understanding LCINS biology at the somatic exome and genome levels, yet the germline contribution remains largely unexplored and large-scale sequencing studies in diverse populations are needed to define germline genetic risk. Furthermore, our understanding of environmental carcinogens continues to evolve, and future directions for research should include the mechanisms driving carcinogenesis mediated by non-tobacco-related exposures, such as environmental pollution, and their interaction with underlying germline variation. The biological distinctions between LCINS and smoking-related lung cancers necessitate a unique approach to diagnosis and treatment, with integration of environmental exposures and both germline and somatic genetics to deliver precision oncology strategies for the treatment and prevention of this increasingly important disease.

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Key points

- The global incidence of lung cancer is decreasing in parallel with declining smoking rates in developed countries; however, the incidence of lung cancer in individuals who have never smoked (LCINS) is stable or increasing.
- LCINS is the eighth leading cause of cancer-related mortality in the USA and the fifth most common cause of cancer-related deaths worldwide.
- LCINS has histological and epidemiological distinctions from smoking-related lung cancers, occurring almost exclusively as adenocarcinomas and most commonly in women and individuals of Asian ancestry.
- LCINS are highly enriched for targetable oncogenic alterations, have low tumour mutational burden and low rates of PD-L1 positivity, and lack mutational signatures, even in patients who report passive, secondhand smoke exposure.
- LCINS development probably involves interactions between genetic risk, mediated by common and rare germline variants, and environmental exposures, including air pollution and particulate matter, with potential opportunities for broader lung cancer screening.
- In the era of precision oncology, the biological underpinnings of LCINS necessitate unique diagnostic and treatment paradigms and warrant consideration of this disease as an important and distinct clinical entity.

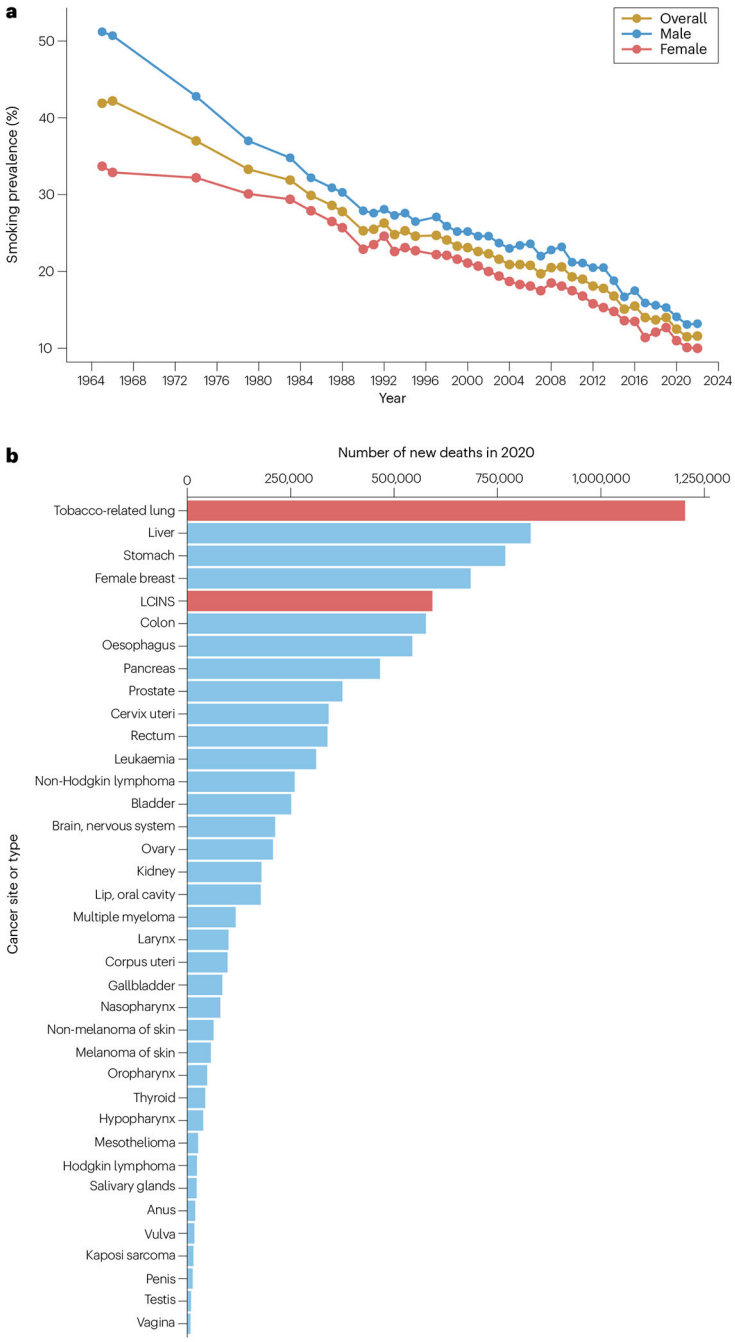

Fig. 1 |. Smoking rates and lung cancer-related deaths.

a, Smoking prevalence in the USA from 1965 to 2022 as the percentage of adults aged ≥18 years who reported currently smoking cigarettes, overall and by sex. The data are derived from the National Health Interview Survey (NHIS) 1965–2018 and 2019–2022 (refs. 2,3,385,386) and are not available for all years. **b**, Estimated number of global deaths attributed to 37 cancer types in 2020 (ref. 6). Smoking-related lung cancer and lung cancer in individuals who have never smoked (LCINS) are shown in red as the first and fifth leading cause of cancer deaths, respectively.

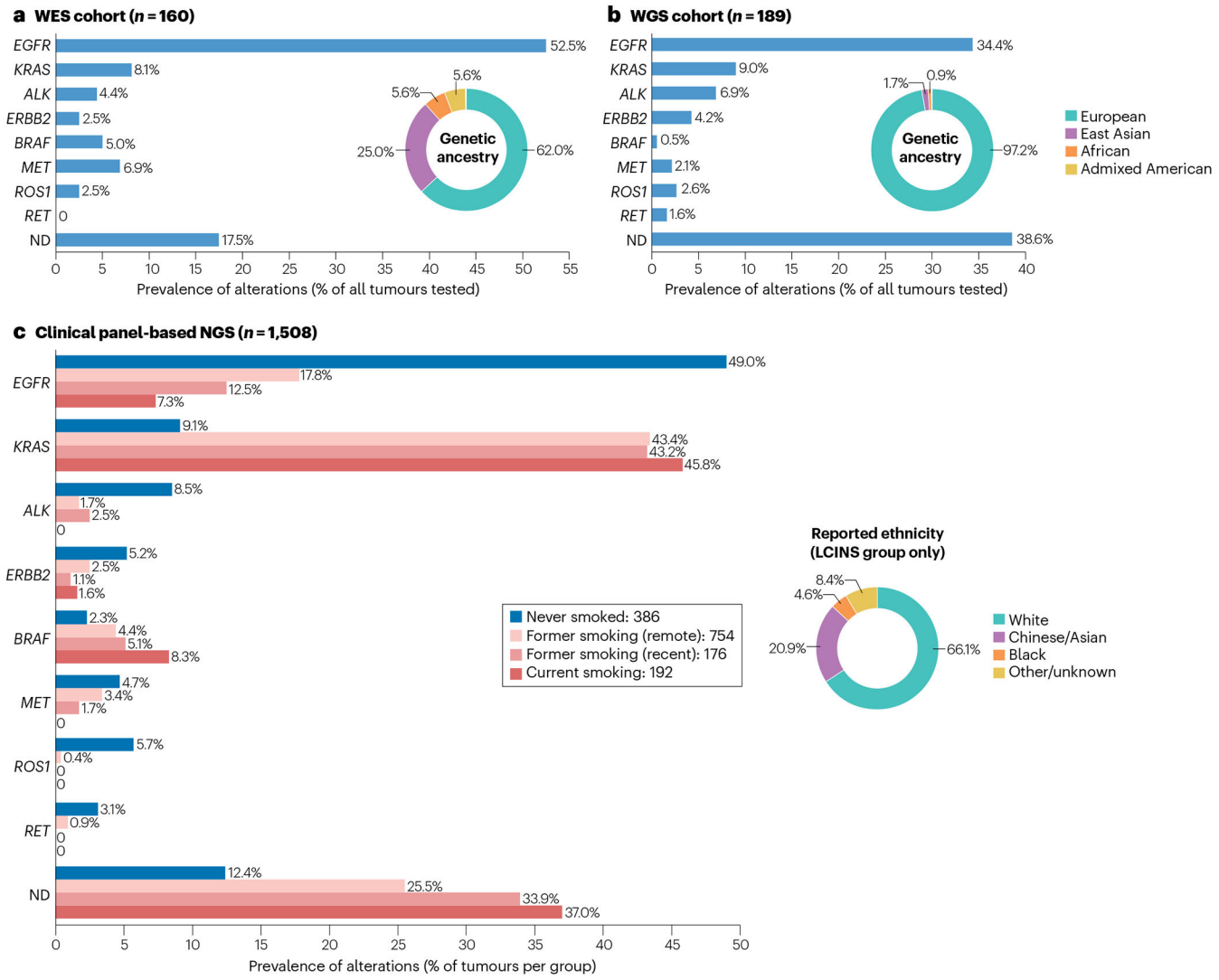

Fig. 2 |. Prevalence of oncogenic somatic driver alterations in LCINS.

Data from somatic profiling studies of lung adenocarcinoma (LUAD) in individuals who have never smoked (LCINS). **a**, Whole-exome sequencing (WES) and RNA sequencing study[7] of 160 samples, at an average depth of 20–30× for WES. The prevalence of each somatic driver alteration was calculated as a composite average using three individual cohorts included in the study, with values weighted proportionally to the number of samples in each cohort. Genetic ancestry was inferred by the authors based on germline sequencing data from matched peripheral blood. **b**, Whole-genome sequencing (WGS) study[78] of 189 samples at an average depth of 85×. Genetic ancestry was inferred by the authors based on germline sequencing data from matched peripheral blood. **c**, Clinical panel-based next-generation sequencing (NGS) data from 1,508 LUADs, collected as part of the non-small-cell lung cancer (NSCLC) cohort of the AACR Project GENIE Biopharma Collaborative[79], across four large academic cancer cancers in North America (Dana-Farber Cancer Institute, Memorial Sloan Kettering Cancer Center, Vanderbilt-Ingram Cancer Center, and Princess Margaret Cancer Centre-University Health Network). Clinical data

available for this cohort include tumour histology, patient self-reported primary ethnicity and cigarette use at time of diagnosis: never smoked; quit smoking >1 year prior to diagnosis (‘former smoking (remote)’); quit smoking <1 year prior to diagnosis (‘former smoking (recent)’); and current smoking. Self-reported primary ethnicity is shown for samples with never-smoking status only. Included for analysis were somatic mutations (*EGFR*, *KRAS*, *ERBB2*, *BRAF* and *MET*) and gene fusions (*ALK*, *ROS1* and *RET*) annotated as ‘putative drivers’ based on prior knowledge (OncoKB[387,388]) and statistical recurrence (Cancer Hotspots[389,390]). The GENIE Biopharma Collaborative Public release is available for download (https://www.synapse.org/#!Synapse:syn27056172/wiki/616601) and can be visualized and analysed using the cBioPortal interface (https://genie.cbioportal.org/study/summary?id=nsclc_public_genie_bpc). Note, wide ranges in the prevalence of particular alterations across studies probably reflect differences in cohort ascertainment (for example, 25.0% versus only 1.7% of patients were of East Asian ancestry in the WES and WGS studies, respectively) and heterogeneity of testing assays used. ND, none of the above alterations detected.

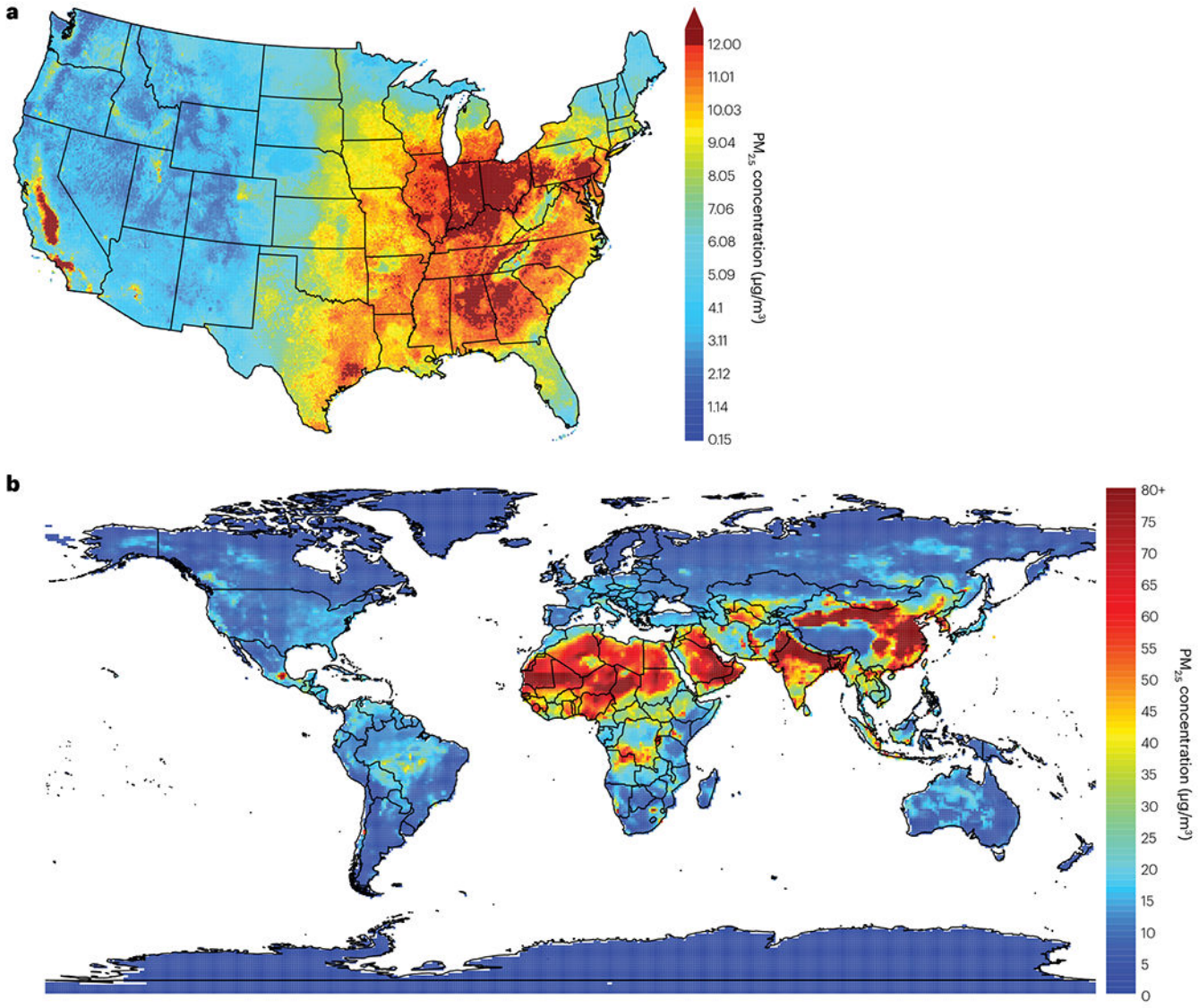

Fig. 3 |. Annual average $PM_{2.5}$ concentrations across the world.

a, Mean annual average concentrations of particulate matter measuring ≤2.5 μm in diameter ($PM_{2.5}$) across the contiguous United States, plotted in 1-km grids, spanning years 2000–2016 (ref. 276). The annual estimates are averages of daily predictions for each year in each grid cell. The current US Environmental Protection Agency annual average primary, health-based national ambient air quality standard for $PM_{2.5}$ is ≤12.0 μg/m^3, with a proposed revision to within 9.0–10.0 μg/m^3 announced in January 2023 (ref. 275). **b**, Mean annual average $PM_{2.5}$ concentrations across the globe, spanning years 2003–2022, according to European Centre for Medium-range Weather Forecasts Atmospheric Composition Reanalysis 4. Performed by the Copernicus Atmosphere Monitoring Service, the reanalysis combines data from modelling studies with observations from across the world into a globally complete dataset[277]. Annual estimates are averages of monthly predictions. The WHO air quality guidelines[273] recommend annual mean $PM_{2.5}$ concentrations of ≤5 μg/m^3.

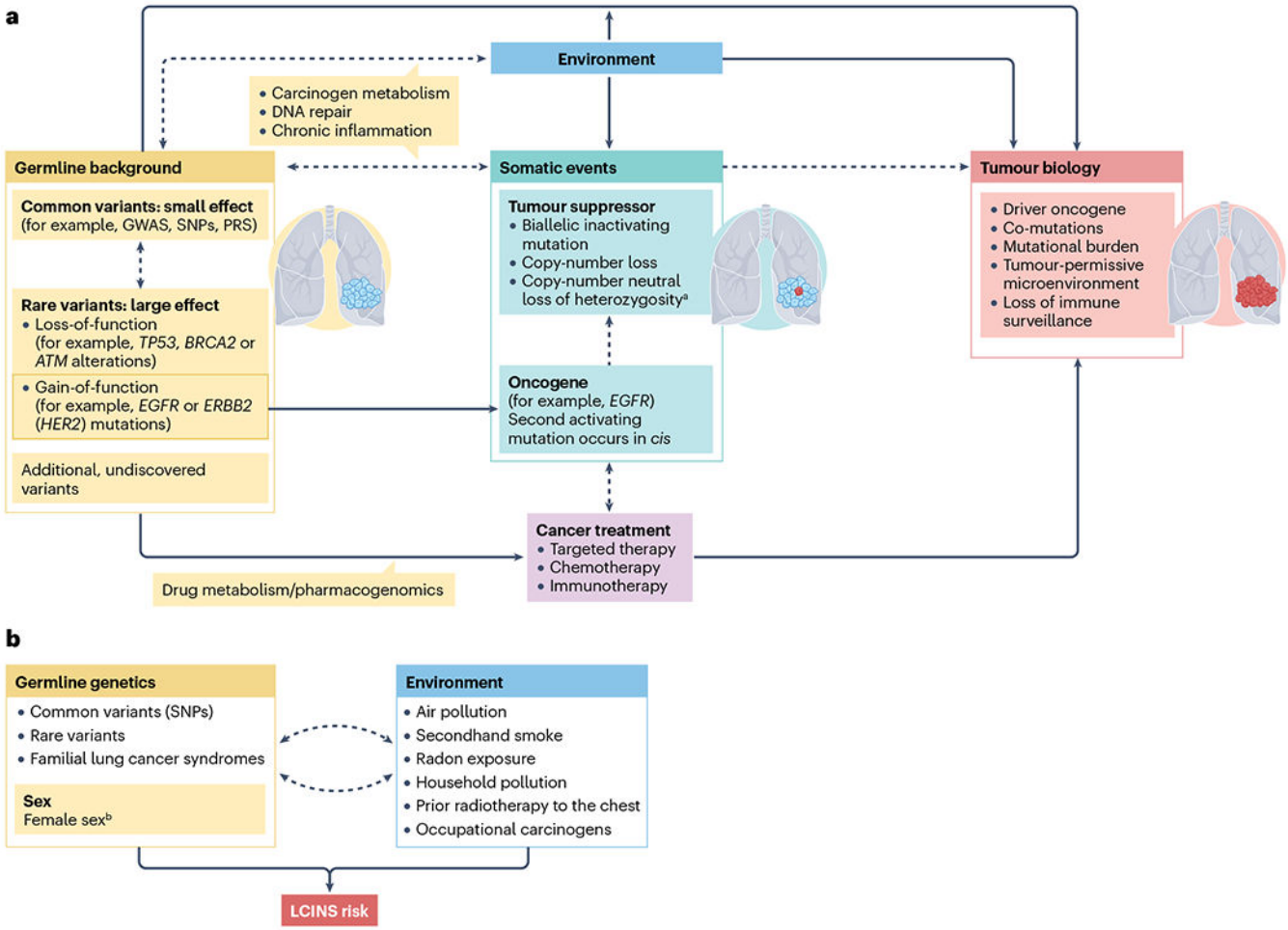

Fig. 4 |. Germline–somatic and gene–environment interactions in the pathogenesis of LCINS. **a**, Model of germline–somatic interactions in lung cancer in individuals who have never smoked (LCINS). Dashed lines and arrows indicate interactions, whereas solid lines and arrows indicate direct processes. Germline variants and acquired somatic alterations can interact to promote cancer development and progression (potential mechanisms are detailed in the main text). Moreover, germline variants affecting carcinogen metabolism, DNA repair and inflammatory processes can interact with environmental exposures and thereby influence the acquisition of somatic alterations and tumour development, and polymorphisms in genes underlying drug metabolism can affect responses to therapy or the development of treatment-related toxicities (the concept of pharmacogenomics). **b**, Risk factors promoting LCINS include environmental exposures such as radon, secondhand smoke, outdoor (air) and indoor (household) pollution, occupational carcinogens, and prior radiotherapy to the chest. Patient-level risk factors include female sex[b], Asian ethnicity and germline risk, the genetic architecture of which consists of common variants of small to moderate effect as well as rare and ultra-rare variants of large effect. Familial lung cancer syndromes are mediated by rare germline mutations in oncogenes such as *EGFR*. Interaction between genetics and environment can occur across any and/or multiple risk factors. GWAS, genome-wide association study; PRS, polygenic risk score; SNP, single-

nucleotide polymorphism. [a]Copy number neutral loss of heterozygosity events can occur at loci harbouring either tumour-suppressor genes or oncogenes. [b]Note, environmental risks related to the socioeconomic and cultural aspects of female gender (such as historically greater exposure to household cooking fumes among women), and/or biological factors related to female sex, might contribute to the effect of female sex.

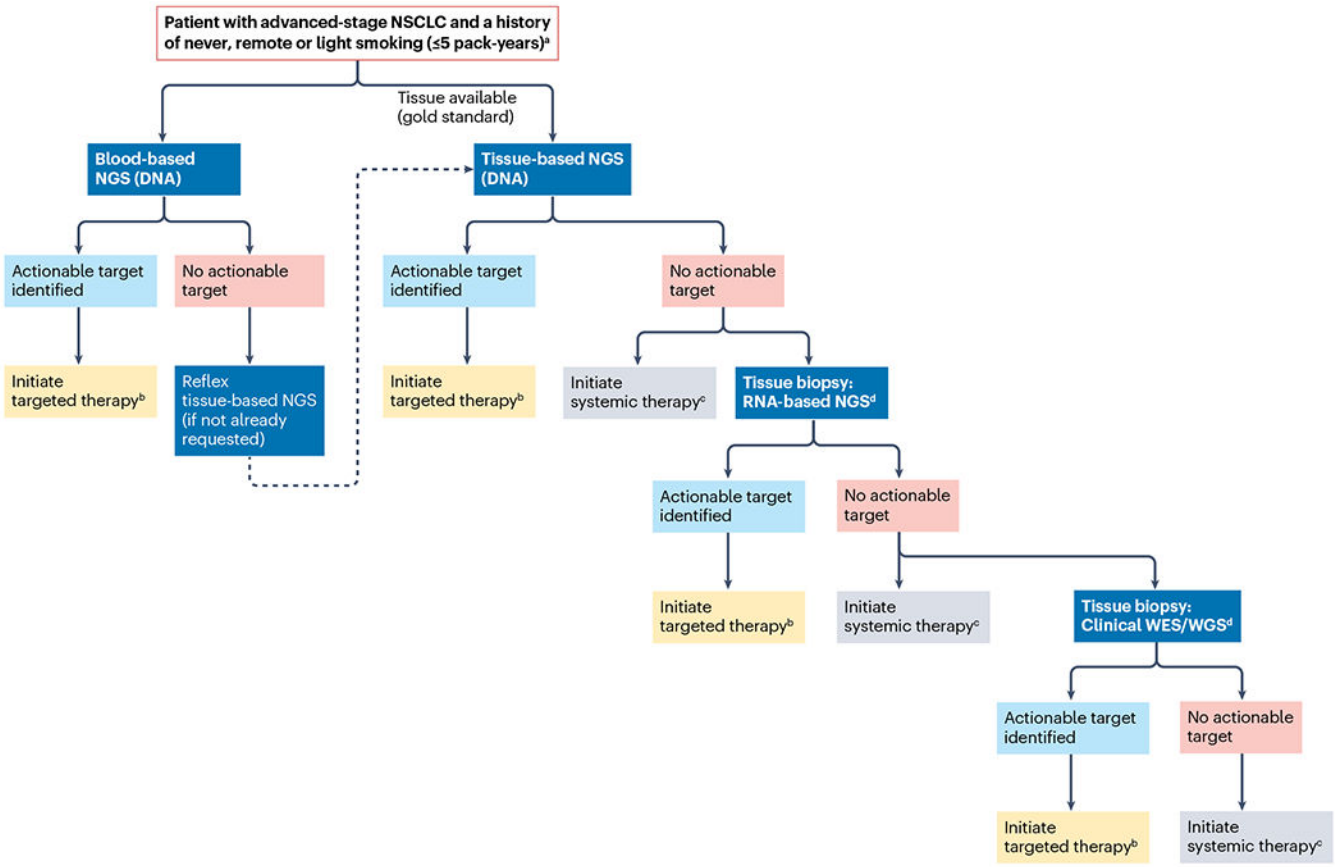

Fig. 5 |. Molecular diagnostic algorithm for advanced-stage LCINS.

The algorithm outlines a sequential approach to evaluating the presence of targetable oncogenic driver alterations in lung cancers in individuals who have never smoked (LCINS) or who have a limited smoking history, which are almost exclusively non-small-cell lung cancer (NSCLC) of adenocarcinoma histology. The National Comprehensive Cancer Network (NCCN) Guidelines[321] recommend that molecular analysis of advanced-stage NSCLC should include assays to identify actionable alterations in *EGFR*, *KRAS*, *ALK*, *ROS1*, *RET*, *ERBB2* (also known as *HER2*), *NTRK1–3, BRAF* (V600E) and *MET* exon 14, for which FDA-approved targeted therapies are available. Emerging therapeutic biomarkers include high-level *MET* amplification, with the current NCCN Guidelines (version 5.2023) noting that thresholds constituting high-level MET amplification are evolving; when next-generation sequencing (NGS) is used, a *MET* copy number of ≥10 is consistent with high-level *MET* amplification and is associated with clinical benefit from MET tyrosine kinase inhibitors. Although NGS is the preferred analytical modality, molecular profiling is defined as broad testing that identifies all relevant clinically actionable biomarkers in either a single assay or a combination of a limited number of assays and, ideally, also identifies emerging biomarkers. WES, whole-exome sequencing; WGS, whole-genome sequencing. [a]Simultaneous blood-based and tissue-based NGS testing recommended, with ideal turnaround times of 7–10 days and 2–3 weeks, respectively. [b]If a matched targeted therapy is not approved in the first-line setting, may consider clinical trials offering first-line targeted therapy versus standard-of-care treatment (for example, NCT05048797

for *HER2*-mutant NSCLC). [c]Clinical decision-making should include consideration of clinicopathological variables such as smoking history, histology, PD-L1 positivity and tumour mutational burden, noting that the majority of LCINS are associated with poor response to immunotherapy. [d]If available, to maximize detection of fusion proteins and emerging targets.

Table 1 |

Somatic features reported for LCINS compared to tobacco-related lung cancers

Feature	LCINS	Tobacco-related lung cancer
Histology	NSCLC; mostly LUAD[1,2]	LUAD, LSCC or SCLC; strongest association with LSCC and SCLC[334]
Targetable driver alterations	Present in 78–92% of LUADs[3–5]	Present in 49.5% of LUADs (mainly *KRAS* mutations)[7]
PD-L1 expression level	Low[36–8],[a]	Highest with current smoking; PD-L1 staining intensity is positively correlated with pack-years of smoking history[136]
TMB	0–3mut/Mb (refs. 3–5,9–13) (median 1.1 mut/Mb)	Up to tenfold higher than in LCINS[131], with a dose–response relationship between pack-years of smoking history and TMB[132]
Genomic signatures	Devoid of tobacco-associated mutational signatures, including LCINS with SHS exposure[3–5]	SBS signature 4[b] (mainly C>A transversions), attributable to misrepair of DNA damage[40,135]; less strongly associated with indel-based signature 3[c] and doublet-base substitution signature 2 (ref. 335); total number of SBS nearly fivefold higher in smoking-related versus non-smoking-related LUADs (mean 12.09 vs 2.65; $P = 2.7 \times 10^{-13}$); total number of indels higher in smoking-related versus non-smoking-related LUADs (mean 0.39 vs 0.14; $P = 7.9 \times 10^{-14}$)[40]

LCINS, Lung cancers in individuals who have never smoked; LUAD, lung adenocarcinoma; mut/Mb, mutations per megabase; NSCLC, non-small-cell lung cancer; SBS, single-base substitution; LSCC, lung squamous cell carcinoma; SCLC, small-cell lung cancer; SHS, secondhand smoke; TMB, tumour mutational burden.

[a]Moderate to high levels of PD-L1 expression have been observed in LCINS with *MET* exon 14 mutations[14,15].

[b]Reliably detectable with targeted panel-based next-generation sequencing assays.

[c]Reliable detection restricted to whole-exome or whole-genome sequencing analyses[336,337]; at present, these mutational signatures are mainly used for investigational purposes with limited use in clinical diagnostics.

Table 2 |

Key genome-wide association studies identifying LCINS risk loci, stratified by population ancestry

Study	Study cohorts: sample size (cases/controls)	Chromosomal region	Reference SNP cluster ID (rsID)	Associated genetic loci	OR (discovery; 95% CI)
European					
Li et al. (2010)[160]	Mayo Clinic: 377/377 MDACC: 328/407 Harvard University: 92/161 UCLA: 91/439	13q31.3	rs2352028	*GPC5*	1.46 (1.26–1.70; $P = 5.94 \times 10^{-6}$)
Wang et al. (2010)338,[a]	Candidate gene study: 259/553	5p15.33	rs4975616	*CLPTM1L–TERT*	0.69 (0.55–0.85; $P = 7.95 \times 10^{-4}$)
Sptiz et al. (2011)252,[a]	Pathway-based (inflammatory) association study: 451/508	12q13.13	rs12809597	*ACVR1B*	0.72 (0.59–0.88; $P = 0.0012$)
Hung et al. (2019)[339]	ILCCO: 3,636/6,295	5p15.33	rs380286; rs31490; rs4975616	*CLPTM1L–TERT*	rs380286: 0.77 (0.72–0.82; $P=5.31\times10^{-16}$) rs31490: 0.77 (0.72–0.82; $P=4.32\times10^{-16}$) rs4975616: 0.78 (0.73–0.83; $P=1.04\times10^{-14}$)
East Asian					
Hsiung et al. (2010)162,[b]	GELAC (Han Chinese): 584/585 GELAC (replication set): 610/560 CAMSCH: 287/287 SNU: 259/293 SWHS: 209/213 WHLCS: 207/207 KNUH: 121/119 KUMC: 95/87 GEL-S: 194/546 NJLCS: 203/203	5p15.33	rs2736100	*CLPTM1L–TERT*	1.54 (1.41–1.68; $P=2.60\times10^{-20}$); 1.62 (1.40–1.87; $P=8.51\times10^{-11}$) when heterozygous; 2.54 (1.95–2.83; $P=3.05\times10^{-19}$) when homozygous
Hosgood et al. (2012)340,[b]	GELAC, CAMSCH, SNU, KUMC, KNUH, SWHS, GEL-S, SLCS, FLCS and TLCS: 3,467 (2,557 LUAD, 309 SCC)/3,787 in total	3q28	rs10937405; rs4488809	*TP63*	rs10937405: 0.80 (LUAD: 0.74–0.87; $P=7.1\times10^{-8}$); 0.82 (SCC: 0.67–0.99; $P=0.037$) rs4488809: 1.16 (LUAD: 1.08–1.24; $P=7.4\times10^{-5}$)
Shiraishi et al. (2012)[341]	Japanese population study: 1,722/5,846	6p21.3	rs3817963	*BTNL2*	1.18 (1.12–1.24; $P=2.7\times10^{-10}$)
		17q24.3	rs7216064	*BPTF*	1.20 (1.13–1.26; $P=7.4\times10^{-11}$)
Lan et al. (2012)163,[b]	FLCCA: 5,510/4,544 (from 14 studies) and 1,099/2,913 (replication set)	10q25.2	rs7086803	*VTI1A*	1.32 (1.24–1.41; $P=5.04\times10^{-17}$)
		6q22.2	rs9387478	*ROS1, DCBLD1*	0.85 (0.81–0.90; $P=7.79\times10^{-8}$)
		6p21.32	rs2395185/ rs28366298	HLA class II region	1.16 (1.09–1.23; $P=2.60\times10^{-6}$)

Study	Study cohorts: sample size (cases/controls)	Chromosomal region	Reference SNP cluster ID (rsID)	Associated genetic loci	OR (discovery; 95% CI)
Ahn et al. (2012)[171]	Korean population study: 446/497 (discovery set) and 434/1,000 (replication set)	18p11.22	rs11080466; rs11663246	*FAM38B (PIEZO2), APCDD1, NAPG*	rs11080466: 0.61 (0.44–0.77; P=2.68×10^{-5}) rs11663246: 0.60 (0.48–0.76; P=1.74×10^{-5})
Kim et al. (2013)175,[b]	Korean population study: 285/1,455 (discovery set), 294/495 (replication set 1) 546/733 (replication set 2)	2p16.3	rs10187911	*NRXN1*	1.47 (1.22–1.78; P<0.001)
Wang et al. (2016)174,[b]	FLCCA: 6,877/6,277 (from 4 studies) and 5,878/7,046 (replication set)	6p21.1	rs7741164	*FOXP4, FOXP4–AS1*	1.18 (1.10–1.26; P=2.05×10^{-6})
		9p21.3	rs72658409	*CDKN2B, CDKN2B–AS1*	0.75 (0.67–0.83; P=1.37×10^{-7})
		12q13.13	rs116101143	*ACVR1B*	0.88 (0.83–0.93; P=2.21×10^{-6})
Shi et al. (2023)[159]	FLCCA: 4,438/4,544 NJLCS: 1,923/3,544 NCC: 3,291/19,910 ACC: 1,471/2,564	2p23.3	rs682888	*DTNB*	0.89 (0.86–0.93; P=4.94×10^{-10})
		3q22.2	rs137884934	*PIK3CB*	0.81 (0.74–0.89; P=6.33×10^{-6})
		4p13	rs117715768	*KCTD8*	1.24 (1.14–1.34; P=4.48×10^{-7})
		4q32.1	rs1373058	*PDGFC*	1.10 (1.05–1.15; P=8.55×10^{-6})
		6p12.1	rs531557	*GCLC*	0.90 (0.87–0.94; P=7.73×10^{-7})
		7q31.33	rs4268071	*GPR37*	1.39 (1.25–1.54; P=7.27×10^{-10})
		10q26.13	rs10901793	*FAM53B, METTL10*	1.10 (1.06–1.14; P=3.14×10^{-7})
		11q12.2	rs174559	*FADS1*	0.91 (0.88–0.94; P=6.10×10^{-7})
		15q21.2	rs764014	*RFX7*	0.91 (0.88–0.95; P=5.75×10^{-7})
		15q21.3	rs71467682	*FGF7, SECISBP2L*	0.91 (0.87–0.95; P=2.46×10^{-6})
		19p13.1	rs116863980	*PALM*	1.31 (1.16–1.47; P=7.94×10^{-6})
East Asian and European					
Shi et al. (2023)[159]	ILCCO multi-ancestry meta-analysis (similar effect sizes observed in both groups): 11,753/30,562 (East Asian) and 11,273/55,483 (European)	2p11.2	rs1130866	*SFTPB*	1.08 (P=1.56×10^{-8})[c]
		4q32.2	rs2320614	*NAF1*	1.08 (P=6.51×10^{-9})[c]
		16q23.3	rs34638657	*MPHOSPH6*	1.09 (P=2.19×10^{-9})[c]
		18q12.1	rs638868	*GAREM1*	1.08 (P=3.60×10^{-8})[c]

The table lists the novel risk loci identified in each study. ACC, Aichi Cancer Center (Japan); CAMSCH, Chinese Academy of Medical Sciences Cancer Hospital; FLCCA, Female Lung Consortium in Asia; FLCS, Fudan Lung Cancer Study (China); GELAC, Genetic Epidemiological Study of Lung Adenocarcinoma (Taiwan); GEL-S, Genes and Environment in Lung Cancer, Singapore study; ILCCO, International Lung Cancer Consortium; KNUH, Kyungpook National University Hospital (South Korea); KUMC, Korea University Medical Center; LCINS, lung cancer in individuals who have never smoked; LUAD, lung adenocarcinoma; MDACC, MD Anderson Cancer Center; NCC, National Cancer Center of Japan Research Institute; NJLCS, Nanjing Lung Cancer Study (China); OR, odds ratio;

SCC, squamous cell carcinoma; SLCS, Shenyang Lung Cancer Study (China); SNP, single-nucleotide polymorphism; SNU, Seoul National University (South Korea); SWHS, Shanghai Women's Health Cohort Study (China); TLCS, Tianjin Lung Cancer Study (China); WHLCS, Wuhan Lung Cancer Study (China); UCLA, University of California Los Angeles (USA).

[a] These studies are candidate gene and pathway-based analyses, which interrogate predefined biological pathways or gene sets; these are distinct from traditional genome-wide association studies and do not require genome-wide significance; therefore, the results should be interpreted with caution.

[b] These studies were focused specifically on women.

[c] No confidence intervals provided in summary statistics.

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Table 3 |

Environmental risk factors for LCINS

Risk factor	Effect summary	Refs.
Radon	Second-leading environmental cause of lung cancer, after smoking, and estimated to account for ~12% of lung cancers in the USA annually; the association of radon with lung cancer was first noted in uranium miners in the 1980s[228,229]; numerous large, global studies have demonstrated an association between prolonged residential radon exposure and lung cancer in the general population; the risk is greatest when combined with smoking[230,234,242] but applies to both smoking and non-smoking populations[244]; the strongest histological association is with SCLC, followed by LUAD[245–247]	226,228–239, 242–247,342
SHS	SHS increases the risk of lung cancer development in individuals who do not smoke by 20–25% and is responsible for ~3,500 lung cancer deaths among non-smoking people in the USA annually[1,13]; other studies are limited but the reported effect sizes are moderate (OR range 1.2–2.1)[153,253–256,343]; no differences in the prevalence of various targetable alterations found in LCINS have been reported based on exposure to SHS[258]; tobacco-related mutational signatures have not been detected in SHS-related LCINS[7,78]	1,7,13,78,153,249–256,258,343
Occupational carcinogens	Elements, such as sulfur, arsenic, beryllium, cadmium, chromium, nickel, plutonium and radon, fumes and particulate matter with a diameter of ≤10μm (PM_{10}) or ≤2.5μm ($PM_{2.5}$), diesel engine exhaust emissions, silica dust, X-rays, and γ-radiation have each been associated with an increased risk of LCINS[281], as have bis(chloromethyl)ether, chloromethyl methyl ether (technical grade), coal-tar pitch and asbestos (all forms, including actinolite, amosite, anthophyllite, chrysotile, crocidolite and tremolite); asbestos is definitively associated with an increased risk of bronchogenic carcinoma and pleural mesothelioma[285,286], with the risk being several-fold higher for lung cancer than for mesothelioma[285,286], although for both, the risk is greatly multiplied when combined with cigarette smoking[286,290–292,344]; silica, diesel exhaust emissions and welding fumes increase the risk of lung cancer independently of smoking and co-exposures[282–284]	281–286,289–294,344,345
Air pollution	Air pollution and fine particles ($PM_{2.5}$) are classified as group 1 carcinogens by the WHO IARC[268,310]; WHO has estimated that ~6% of outdoor air pollution-related premature deaths in 2016 were due to lung cancer[268]; associations with lung cancer risk and mortality have been demonstrated in individuals who have smoked and those who have not (HR < 2)[265,267,271,272], and air pollution-associated lung cancer risk is probably influenced by underlying genetic susceptibility[265,278]; $PM_{2.5}$ levels positively correlated with rates of *EGFR*-mutant lung cancer in England, South Korea and Taiwan[279]	261–265,268,276–279,346
Electronic cigarettes/ vaping	The carcinogenic potential of electronic cigarette/vaping particles is not currently known and is probably dependent on the composition of aerosolized liquid, the device and user habits[302–304]; long-term follow-up studies are required to determine any lung cancer risk	302–308,347–349
Household use of solid fuels and high-temperature frying	Fumes and particulate matter generated from cooking and heating contain group 1 (carcinogenic) or group 2 (likely carcinogenic) substances as defined by the WHO IARC; dose–response relationships between reported exposure to cooking oil fumes and lung cancer risk have been demonstrated; in Chinese non-smoking women, the ORs are as high as 6.15 in the highest exposure groups (higher with deep frying versus stir-frying and in homes with poor ventilation)[311–313]; indoor burning of coal, wood and other biomass is associated with an increased risk of lung cancer with ORs <2, with greater levels of risk in women than in men[315,316,350]	310–316,350
Diet	No consistent data exist that implicate dietary differences as being associated with lung cancer risk; primary chemoprevention studies focused on lung cancer have not demonstrated benefit from dietary supplements, although some studies have shown an association between β-carotene supplementation and a reduced risk of lung cancer in men who have smoked[351–353]	351–355
HRT	Findings regarding the association between HRT and lung cancer risk are mixed; data from the Women's Health Initiative trial demonstrated no statistically significant increase in the risk of lung cancer with either oestrogen–progestin or oestrogen-only HRT[356–358]; however, results of the Vitamins and Lifestyle study indicate an increased risk of lung cancer with oestrogen–progestin HRT after adjusting for smoking status (HR 1.48 if exposed to ≥10 years oestrogen plus progestin)[359]	78,356–364
Prior and/or chronic lung disease	A history of lung disease (COPD, pneumonia, tuberculosis or interstitial lung disease) is associated with an increased risk of lung cancer[365–370], although the associations are confounded by tobacco smoking and other environmental exposures; an elevated lung cancer risk associated with emphysema, pneumonia and tuberculosis has been observed consistently in white men[367]; the underlying mechanisms are presumed to be related to chronic inflammation and parenchymal lung injury; whether autoimmune diseases are associated with an increased risk of developing lung cancer in individuals who do not smoke remains unclear	365–375

Risk factor	Effect summary	Refs.
Recreational and illicit drugs	Whether habitual smoking of marijuana or cocaine use increases the risk of lung cancer is unclear owing to confounding by tobacco smoking and/or insufficient follow-up time; opium has been classified as a group 1 carcinogen after smoking or ingestion of this drug was associated with the development of lung cancer among individuals in Golestan province, Iran (HR 2.2)[376]; the lung cancer risks associated with derivatives, such as heroin, morphine, codeine and fentanyl, have not been evaluated	376–382
Prior radiotherapy to the chest	Chest irradiation increases the risk of second primary lung cancer, with the greatest risk in combination with tobacco smoking; for example, a high risk of secondary lung cancer has been demonstrated in individuals who received prior radiotherapy for Hodgkin lymphoma (RR 2.6–7.0), particularly those treated after ≥45 years of age, with chemotherapy having an additive effect[383]; lung cancer risk increases over time up to 20–25 years after radiotherapy; similar observations have been reported in breast cancer survivors, with a tenfold higher lung cancer risk in patients who received radiation for invasive breast cancer versus those who did not[384]	383,384

COPD, chronic obstructive pulmonary disease; HRT, hormone replacement therapy; IARC, International Agency for Research on Cancer; LCINS, lung cancer in individuals who have never smoked; LUAD, lung adenocarcinoma; SCLC, small-cell lung cancer; SHS, secondhand smoke.