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Lung Cancer in Never Smokers

Ping Yang, M.D., Ph.D.¹

¹Department of Health Sciences Research, College of Medicine, Mayo Clinic, Rochester, Minnesota.

Abstract

Lung cancer in never smokers (LCINS) has lately been recognized as a unique disease based on rapidly gained knowledge from genomic changes to treatment responses. The focus of this article is on current knowledge and challenges with regard to LCINS expanded from recent reviews highlighting five areas: (1) distribution of LCINS by temporal trends, geographic regions, and populations; (2) three well-recognized environmental risk factors; (3) other plausible environmental risk factors; (4) prior chronic lung diseases and infectious diseases as risk factors; and (5) lifestyles as risk or protective factors. This article will also bring attention to recently published literature in two pioneering areas: (1) histological characteristics, clinical features with emerging new effective therapies, and social and psychological stigma; and (2) searching for susceptibility genes using integrated genomic approaches.

Keywords

Lung cancer; never smokers; environmental risk factors; genetic predisposition; molecular target therapy

OVERVIEW

Never smokers in the context of lung cancer have been commonly defined as people who have smoked less than 100 cigarettes in their lifetime.¹ In spite of the public impression that the majority of lung cancer patients are smokers, over one-half of lung cancer cases diagnosed today are never smokers or former smokers, and women are disproportionately affected among never smokers. Physicians and scientists have long recognized that lung cancer in never smokers (LCINS) is a very different disease than lung cancer in smokers. A few comprehensive reviews of the biology, diagnosis, and treatment of LCINS have been recently published^{1–5} and serve as the tangible background of epidemiology and risk factors described here.

DESCRIPTIVE EPIDEMIOLOGY OF LCINS: PAST AND PRESENT

Long before the advent of cigarette smoking, primary lung cancer was first recognized as a distinct disease in 1761^{6,7} and was further described in different aspects 50 years later in 1810.^{7,8} Almost another century later between 1899 and 1911, diagnosing lung cancer in living patients was still rare; even autopsy-identified cases were uncommon (i.e., fewer than 1/1000).^{9–12} During the 20th century, population-based data on lung cancer rates (incidence or mortality) among men in Western countries were dominated by the effects of active

cigarette smoking; therefore, by the early 1930s when national mortality statistics were first reported, few data were available for never smokers. Because few women actively smoked during that time, population data on lung cancer in women largely reflected the background rates.¹³ Since the 1930s in the United States and the world, lung cancer rates exponentially increased (peaked at 100/100,000 for men in the late 1980s and currently a plateau at 55/100,000 for women) as a consequence of pandemic cigarette smoking, but remain relatively stable in never smokers (~10 to 20/100,000).^{3,14} More recent data between 1992 and 2000 from the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort of 519,978 participants, the age-standardized incidence rates of LCINS (aged 35 to 79 years) were 6.6 and 7.1 per 100,000 person-years for men and women, respectively.¹⁵ Differences in incidence estimates across studies are more likely due to the variation in the definition of never smokers, specific populations for standardized adjustments, and surrogate measures through mortality data.

As highlighted by Samet et al and Subramanian et al,^{3,16} LCINS increases with age but is similar between men and women. Little evidence supports the suggested trend that lung cancer risk is increasing over time in the general population outside the context of tobacco smoking. Large geographical differences in lung cancer risk in never smokers exist; the reported lowest rates are in Africa and India, whereas the highest rates are in Far East Asian countries.^{3,16} In the United States, among patients with non-small-cell lung cancer (NSCLC) that was diagnosed younger than 40 years of age, there is a greater representation of African Americans, Asians, or Pacific Islanders.^{3,16}

CURRENT KNOWLEDGE REGARDING RISK FACTORS

Radon gas and its progeny were the first identified environmental causes of lung cancer in eastern Europe¹⁷; the original case report of respiratory malignancy in underground miners was published in 1879.¹⁸ Numerous subsequent epidemiological studies,¹⁹ clearly in never smokers, were Navajo uranium miners in the United States; cumulative evidence over the decades points to the relative risk of lung cancer as high as greater than 20 over the general population.²⁰⁻²³ Beyond radon and miners, public awareness and scientific investigations of why never smokers in the general population develop lung cancer have been increasing in the past 3 decades.

Secondhand smoking (SHS), residential radon, and indoor air pollution are the top three environmental factors that have been hypothesized, studied, and reported. In the United States, ~20% of LCINS could be contributed to SHS with varied estimated risk ratios (RRs) or odds ratios (ORs) at 1.2 to 2.0^{24,25}; SHS in childhood (before age 16) significantly increases the risk of squamous-, small- and large-cell carcinomas combined (OR = 2.1, 95% CI, 1.0 to 4.3).²⁶ Up to 12% of LCINS could be attributed to indoor residential radon residues with varied estimated RRs over 3.0.^{27,28} In Asian countries, indoor air pollution (combustion of coal and biomass, and cooking fumes in the household) is considered the leading risk factor in women.²⁹ In Germany, second to cigarette smoking, exposure to indoor radon and its decay products is the leading cause of lung cancer in the general population, with an estimated 8 to 16% increased risk for every 100 Bq/m³.³⁰

Other reported and suggested environmental risk factors among never smokers are plausible but with insufficient or inconsistent evidence; these include outdoor air pollution, ionizing radiation from radiation therapy and atomic bomb exposure, and known and suspected occupational agents containing carcinogens.³ The available evidence does not allow accurate risk estimation in never smokers only, exemplified by a newly published meta-analysis of painters.³¹

Preexisting chronic lung diseases have been studied in association with lung cancer risk, predominantly among smokers and a few separately in never smokers, including asthma, idiopathic interstitial disease, fibrotic disorders, emphysema, and chronic obstructive pulmonary disease (COPD).^{3,32} Chronic bronchitis in never-smoking women in Yunnan, China, where exposure to indoor smoky coal combustion is common, has been associated with increased lung cancer risk.³³ Patients with COPD, emphysema, idiopathic pulmonary fibrosis, or other fibrotic disorders are at increased risk for lung cancer,³⁴⁻³⁷ but this risk has not been clearly defined in never smokers.³⁸

History of infectious diseases, such as tuberculosis (TB), human immunodeficiency virus (HIV), Epstein-Barr virus (EBV), and human papillomavirus (HPV), and infections with *Chlamydia pneumoniae*, *Microsporum canis*, and *Helicobacter pylori* have been suspected to increase risk for lung cancer. Except for tuberculosis, results have not been conclusive with regard to LCINS.^{29,39-44} One study found that, compared to those without TB, female never smokers with TB had approximately an eight-fold increase in lung cancer risk but not in smokers.⁴⁵ Another study reported EBV or HPV being unlikely to be important etiological agents in lung adenocarcinoma, regardless of smoking status.⁴⁶

Regarding reproductive history and hormonal supplements, both endogenous and exogenous, estrogen may be involved in the etiology of lung cancer.⁴⁷⁻⁴⁹ Pains or mental tension related to menses and quantity of menstrual flow were reported to be inversely associated with LCINS²⁶; hormone replacement therapy may increase LCINS for middle-aged women⁵⁰; and oral contraceptives may reduce this risk, but likely with marginal public health benefit.^{51,52}

Lifestyle, dietary patterns and supplements, and physical activity have been explored as risk or protective factors for developing LCINS in the past 10 years. An expert panel from the World Cancer Research Fund and the American Institute for Cancer Research concluded that fruits and foods containing carotenoids and isoflavone likely protect against lung cancer. Limited evidence suggests nonstarchy vegetables and selenium to be protective against lung cancer; and inconsistent evidence suggests high-dose retinol supplements, consumption of red meat, processed meats, total fat, and butter to be risk factors of lung cancer.^{26,53-57} Wine drinking at higher frequency than once per month may reduce the risk of adenocarcinoma (OR = 0.46, 95% CI, 0.23 to 0.92).²⁶ Increased physical activity has been associated with decreased lung cancer risk, but this is mostly reported in smokers.⁵⁸⁻⁶⁰ A recent study has evaluated lung cancer mortality in relation to cardiorespiratory fitness (CRF) in 38,000 men who were 20–84 years of age, without history of cancer, and received a preventive medical examination at Cooper Clinic in Dallas, Texas, between 1974 and 2002. CRF was quantified as maximal treadmill exercise test duration and was grouped for analysis as low, moderate, and high. After adjustment for age, examination year, body mass index, smoking, drinking, physical activity, and family history of cancer, lung cancer risk was significantly lower in moderate or high CRF groups than in the low group, regardless of smoking status but more pronounced in smokers.⁶¹

Histopathological and Clinical Features: Distinctions from Smokers

In the search for causes and biological mechanisms of LCINS, understanding the histopathological and clinical features may reveal important clues. A temporal trend has long been observed in the distribution of lung tumor histological type (i.e., shifting from squamous cell carcinoma to adenocarcinoma).^{62,63} This trend has been attributed to the substantial changes in the characteristics of cigarettes and the patterns of deposition and dosages of carcinogens inhaled.⁶⁴ Noted in never smokers, adenocarcinoma has always been the predominant histological type with varied percentage of squamous cell carcinoma by sex and exposure history to secondhand smoke.⁶⁵⁻⁶⁷ Changes in subtypes within a histological

main type (e.g., adenocarcinoma among never smokers) have not been adequately studied.⁶⁸ Because never smokers tend to develop adenocarcinoma, there has been a viewpoint that adenocarcinoma of the lung is weakly or not associated with cigarette smoking.⁶⁹ If this were true, one would expect that lung cancer before the cigarette smoking era would have been primarily adenocarcinoma. However, one of the earliest published documents (1902) that reported histological subtypes of primary lung cancer on 50 consecutive cases reported 32 (64%) being squamous cell carcinoma, two (4%) adenocarcinoma, and 16 (32%) other lung cancer types. Thus adenocarcinoma might not be the predominant lung cancer type in the absence of tobacco smoke,¹² implying that beyond the histological type, lung cancer may not be the same disease among never smokers before and during the pandemic era of cigarette smoking.

HETEROGENEOUS NATURE OF ADENOCARCINOMA: REVISITING BRONCHIOLOALVEOLAR CARCINOMA

Looking into the heterogeneous nature within lung adenocarcinoma, a subtype, namely bronchioloalveolar carcinoma (BAC) is disproportionally more common in never smokers, women, and Asians^{70,71}; patients with BAC experience much better prognosis than patients with other subtypes of adenocarcinoma and may require a different management guideline from other NSCLC patients.^{71,72} As shown in a study of 78 pure BAC cases diagnosed and treated at Mayo Clinic between 1997 and 2008, 1-year and 5-year survival rates were 94.8% and 83.5%, respectively,⁶⁸ supporting that genuine pure BAC may be considered more similar to atypical adenomatous hyperplasia.⁷¹ To fully distinguish and classify pure BAC remains challenging pathologically but necessary for two major reasons: not to have ambiguity in aggressively treating invasive adenocarcinoma and to avoid overtreating a noninvasive disease.

Equally important, understanding the unique and overlapping biological basis between BAC and adenocarcinoma could provide useful markers in predicting the aggressiveness of BAC tumors and adenocarcinomas with a prominent BAC component. Promising markers began to emerge 2 decades ago, including DNA methylation of the glutathione S-transferase P1 gene (GSTP1), cyclin-dependent kinase inhibitor 2A [p16(INK4a)], Ras association domain family member 1 (RASSF1A), and Cadherin 13, H-cadherin (heart) gene (CDH13)^{73,74}; mutation of epidermal growth factor receptor (EGFR), p53, and K-ras⁷⁵⁻⁸²; loss of heterozygosity (LOH) on chromosome 3p, 5q, 9p, and 17p^{78,79,83}; and patterns of global tumor gene expression profiling⁸⁴ (all of which had relatively small sample sizes) were lacking smoking-specific information or showed inconsistent findings. A recent review⁸⁵ captured significant genotype–phenotype correlations between EGFR mutations and the presence of a BAC component, a micropapillary pattern, and the hobnail cell type; patients with these pathological features might benefit from therapy with EGFR tyrosine kinase inhibitors (EGFR-TKI). To conclude, more comprehensive and systematic research is required at multiple genomic levels to achieve the goal of differentiating tumor nature in accordance with pathological and clinical features of LCINS.

THERAPEUTIC MOLECULAR TARGETS: PATIENTS' SPECIFIC TREATMENT OPTIONS

Besides etiology and tumor histology, clinically significant differences between never smokers and smokers have been consistently recognized in terms of prognosis and response to therapy,⁸⁶⁻⁸⁸ with a few exceptions.⁸⁹ Although they usually present at an advanced stage with nonspecific symptoms, never smokers have a better natural history and prognosis with therapy than smokers if their tumors contain EGFR mutation (L858R) and they undertook EGFR-TKI treatment,^{1,90-92} particularly among female patients with adenocarcinoma.⁹³ In

addition to tumor specimens, the EGFR mutations in the serum and the pleural effusion from advanced NSCLC patients can be detected and clinically useful.⁹⁴ Erlotinib, an EGFR-TKI drug, is a standard of treatment for metastatic NSCLC after failure of first-line therapy. Grade 2 to 3 skin toxicity is a sentinel response indicative for significantly prolonged progression-free survival (PFS) and overall survival (OS).⁹⁵ Gefitinib, a small molecule that prevents adenosine triphosphate (ATP) binding in the tyrosine kinase domain of the EGFR, has been demonstrated to be superior to carboplatin/ paclitaxel in a phase III clinical trial (the IRESSA Pan-Asia Study) as first-line treatment for pulmonary adenocarcinoma among never smokers or former light smokers in East Asia.⁹⁶ Gefitinib is anticipated to be used in pretreated and selected chemotherapy-naïve patients with advanced NSCLC and with the presence of an EGFR mutation.⁹⁷

Deeper and Broader Command in EGFR-TKI-Based Therapy: Responses, Resistance, Toxicities, and Remedies

The other side of the successful story of EGFR-TKI-based therapy is that the majority (over 80%) of unselected NSCLC patients do not respond, and patients who responded initially invariably relapse later with resistant disease. Therefore, EGFR-specific TKI drugs, as single agents, will unlikely make a high impact on curing lung cancer.⁹⁸ Acquired resistance is defined as systemic progression of disease⁹⁹ during continuous treatment with gefitinib or erlotinib within the last 30 days, and no intervening systemic therapy.¹⁰⁰ Three challenges to overcome resistance to this group of promising drugs are how to timely and effectively (1) predict true responses, (2) prevent acquired resistance from occurring, and (3) defy resistance. The optimal alternative therapeutic approach after a failed one remains to be defined.

Various predictive markers have been reported beyond the primary mutation, including secondary mutations of EGFR (T790M, S768I, and V769L), cMET (mesenchymal-epithelial transition factor) amplification, EGFR gene copy numbers and status of ligands, and changes in other HER (herceptin) family genes or molecules downstream to EGFR including K-ras or AKT (protein Kinase β -alpha).¹⁰¹⁻¹⁰⁵ Other mechanistic markers include epithelial to mesenchymal transition,¹⁰⁶ and higher expression levels of E-cadherin.^{107,108} To utilize these molecular markers in predicting responses, resensitizing and enhancing EGFR-TKI treatment outcomes are under rapid development.

Imaging approaches may offer early identification of tumor response in EGFR-dependent NSCLC. One has been reported, namely 3'-Deoxy-3'-[(18)F]-fluoro-L-thymidine ([18F]FLT) [(18F)FLT positron emission tomography (PET) imaging has been presented as one appropriate method.¹⁰⁹

Acquired EGFR-TKI resistance should be managed assertively and properly. Options currently in practice include using erlotinib as salvage treatment after failure to gefitinib,^{110,111} taxane-based regimens,¹¹² and single-agent pemetrexed.¹¹³ Promising alternatives have been actively investigated and include MET small molecule inhibitor, SU11274, which targets EGFR-T790M mutation¹¹⁴ (an irreversible EGFR TKI BIBW-2992) and the EGFR-specific antibody cetuximab.¹¹⁵ Other alternatives include receptor tyrosine kinase pathways, such as insulinlike growth factor 1 receptor (IGF-1R) and fibroblast growth factor receptors (FGFRs) (with high degree of homology with vascular endothelial growth factor receptors [VEGFRs] and platelet-derived growth factor receptors [PDGFRs]).⁹⁸ Finally, hsp90 inhibitors (e.g., 17-allylamino-17-demethoxygeldanamycin or 17-AAG) have been demonstrated to be effective to treatment de novo and acquired resistance to EGFR TKIs.¹¹⁶

Although systemic chemotherapy is usually avoided during whole-brain radiation therapy (WBRT) to minimize or avoid toxicities, concurrent administration of erlotinib or gefitinib has been practiced. Gefitinib treatment for never smokers with adenocarcinoma and asymptomatic synchronous brain metastasis showed promising antitumor activity against both intracranial and extracranial tumors.¹¹⁷ However, serious toxicity related to erlotinib was reported in a retrospective evaluation of seven cases; three patients responded, yet three deaths occurred without clear signs of disease progression. Unanticipated severe toxicities include grade 3 hepatotoxicity, hyponatremia, mental status changes, grade 3 to 4 thrombocytopenia, and grade 4 neutropenia with sepsis.¹¹⁸ The benefits and toxicities of erlotinib during WBRT need to be thoroughly assessed with prospective trials.

In contrast to most aspects of lung cancer where most of what is known is among smokers, the mutation status and clinical relevance of EGFR in smokers and male patients are much less clear. Smokers do carry EGFR mutations, and a decreased EGFR mutation rate with increased smoking dose was observed in a Korean study: 48.0% in never smokers, 23.1% in former smokers, and 11.4% in current smokers.¹¹⁹ Mutations in exon 19 or 21 were associated with females ($p < 0.0001$), never smokers ($p < 0.0001$), and adenocarcinoma ($p < 0.0001$); whereas, mutations in exon 20 were more common in smokers. In virtually all clinical trials published to date, randomization in design and analysis of outcome by smoking status have not been reported.

Tale of Anaplastic Lymphoma Kinase

The fusion between echinoderm microtubule-associated protein-like 4 (EML4) and anaplastic lymphoma kinase (ALK), through a small inversion within chromosome 2p, has recently been identified in a subset of lymphoma and NSCLC patients.^{120,121} Other fusion partners of ALK include nucleophosmin (NPM), tropomyosin 3 (TPM3), 5-aminoimidazole-4-carboxamide ribonucleotide formyltransferase/IMP cyclohydrolase (ATIC), TRK-fused gene (TFG), cysteinyl-tRNA synthetase (CARS), and clathrin, heavy chain (Hc) (CLTC).¹²² The EML4-ALK fusions are mutually exclusive with mutations in the EGFR, KRAS, and v-erb-b2 erythroblastic leukemia viral oncogene homolog 2 (ERBB2) genes,¹²³ except one case was reported to have concurrent deletion in EGFR exon 19 and fusion of EML4-ALK in a Chinese woman with an adenocarcinoma.¹²² The EML4-ALK fusion appears to be tightly associated with a higher level of ALK mRNA expression but not EML4 expression.¹²² EML4-ALK is oncogenic both in vitro and in vivo, and ALK kinase inhibitors are quite effective in preclinical model systems and have entered clinical development. Remarkably, clinical efficacy has been observed in NSCLC patients harboring EML4-ALK translocations¹²¹; these patients are more likely to be younger men who were never or light smokers with lung adenocarcinoma.¹²⁴ There is a trend toward improved survival for patients with the EML4-ALK fusion; but an opposite trend is found in another study focusing on never smokers.^{122,125} However, these patients do not benefit from EGFR TKIs and may benefit from ALK-targeted agents.^{124,126}

SOCIAL AND PSYCHOLOGICAL STIGMA: SIMILARITIES TO SMOKERS

The well-recognized stigma of lung cancer is directly related to cigarette smoking. That is, the unfavorable public sentiment toward the medical cost burden and lost productive lives due to smoking has led to the common perception that lung cancer is self-inflicted, and affected patients are blamed. A group of researchers examined the effects of an individual's smoking status on social and psychological aspects of lung cancer, as summarized by Raleigh.¹²⁷ Interestingly, never smokers with lung cancer did not differ from smokers with the disease in major social and psychological stigma. The social stigma that lung cancer is a preventable disease affects never smokers, who felt unjustly blamed for their illness and

were assumed to be smokers. The psychological impact of having lung cancer included feelings of guilt and depression, the same for both smokers and never smokers.¹²⁷

Lung Cancer Susceptibility Genes Found through Integrated Genomic Research

In spite of the exceptionally high contributable risk of tobacco smoke, genetic susceptibility to lung cancer development has been recognized for more than 50 years. Two important pieces of evidence suggesting an inherited predisposition are (1) lung cancer only develops in a minority of heavy and long-term smokers, and (2) it aggregates in families independent of smoking.¹²⁸ However, identifying and characterizing lung cancer-causing genes have been hindered by difficulty in assembling enough informative pedigrees (for genetic linkage studies of rare and high-penetrance genes) or recruiting sufficient biological samples from never smokers (for case-control studies of common and low-penetrance genes). Even in the genomic era with effective high throughput technology and feasible genomewide association strategies, fewer than 10 studies have been reported to specifically identify lung cancer susceptibility genes.¹²⁹ Most of these studies were in primarily smokers; nonetheless, candidate genes identified from these studies are important in understanding inherited predisposition to developing lung cancer and in elucidating mechanistic interactions and causal roles between genetic background and environmental exposures.

RARE AND HIGH-PENETRANCE GENES

In 2004, the first major susceptibility locus influencing lung cancer risk was localized to chromosome 6q23–25 using a genomewide linkage analysis of 52 extended pedigrees¹³⁰ and was refined to confer particularly higher risks to never and light smokers.¹³¹ In this chromosome region, *RGS17* was identified as the novel candidate gene in familial lung cancer,¹³² and *p34* was a novel tumor suppressor gene in sporadic lung cancer¹³³; roles of these two genes in never smokers need to be defined.

COMMON AND LOW-PENETRANCE GENES

Between 2007 and 2009, eight genomewide association (GWA) single-nucleotide polymorphisms (SNP) studies have reported association between chromosome loci and lung cancer susceptibility in samples of primarily smokers.^{134–141} Of the five top candidate SNPs, two (rs402710 and rs2736100) are located in chromosome 5p15.33, containing the human telomerase reverse transcriptase (*TERT*) gene and the cleft lip and palate transmembrane 1 like (*CLPTM1L*, alias *CRR9*) gene; the overall estimated allelic ORs are under 1.2.¹³⁷ Two of the remaining three SNPs (rs8034191 and rs16969968) are located in chromosome 15q25 containing six known genes [allelic ORs between 1.21 and 1.45]¹³⁵; three of the six genes encode nicotinic acetylcholine receptor subunits (*CHRNA5*—cholinergic receptor nicotinic α 5, *CHRNA3*—cholinergic receptor nicotinic α 3, and *CHRNA4*—cholinergic receptor nicotinic β 4); the other three genes are *IREB2* (iron-responsive element-binding protein 2), *PSMA4* (implicated in DNA repair), and aminoglycoside phosphotransferase domain-containing protein 1 (LOC123688, unknown function). The fifth top SNP (rs4324798) is located in chromosome 6p21.33 within an extended region near the major histocompatibility complex containing more than 20 genes, and five validation studies provided evidence of association with lung cancer risk, at an OR of 1.28 (1.16 to 1.40).¹³⁵ However, two small subsets of never smokers did not support the observed SNP associations in smokers,^{139,142} and additional validation studies are required to elucidate whether nicotine dependence genes are in the causal pathway to lung cancer in never smokers.

In 2010, the first GWA study reported genetic variants at chromosome 13q31.3 being associated with susceptibility to LCINS through regulating *GPC5* expression.^{143–145} Glypican 5 (*GPC5*) is a member of the glypican gene family and has eight exons encoding

572 amino acids¹⁴⁶; glypicans are a family of heparan sulfate proteoglycans (HSPGs) that are widely distributed in mammalian tissues and interact with many proteins, including growth factors, chemokines, and structural proteins of the extracellular matrix to influence cell growth, differentiation, and the cellular response to the environment.¹⁴⁷ Landi et al performed a meta-analysis, combining previously published data from GWA studies, supporting the association between a SNP rs2352028 (representing the GPC5 gene) and lung adenocarcinoma risk¹⁴³⁻¹⁴⁵; however, this meta-analysis included very heterogeneous studies: one had smokers in the control group, two had different definitions of “never smokers,” two had fewer than 40 cases and one had a case-control ratio over 1:170, and three had no or minimal data on potential confounders. To validate (or refute) a candidate SNP that has gone through discovery and replication in four independent studies requires an adequately powered study using more refined cases and controls, with complete epidemiological data (e.g., passive smoking, prior COPD diagnosis, and family history of lung cancer) to control for potential biases in the initial results.¹⁴³⁻¹⁴⁵

INTERACTIONS BETWEEN ENVIRONMENTAL AND GENETIC FACTORS

Molecular epidemiology has been thriving in cancer etiologic research, particularly in dissecting how genetic factors modify host responses to environmental insults. A relatively common genotype, as normal variants or polymorphisms, can change the physiological response to carcinogens and can modify meaningfully the cancer burden in populations, even at a low level of exposure to an environmental risk factor. The classic showcase of gene–environmental interaction is the xenobiotransformation system (activating and detoxifying metabolic pathways) genetic polymorphisms and exogenous carcinogen exposure in the causes of LCINS.¹⁴⁸ For example, the germline variants in genes whose products activate [cytochrome P450 1A1 (CYP1A1)] and detoxify [glutathione S-transferases M1 (GSTM1) and T1 (GSTT1)] chemical carcinogens. For carcinogen activating enzymes, there is no increase in risk of LCINS for CYP1A1 Msp I genotypes, with or without SHS exposure history.¹⁴⁹ Among genetic polymorphisms of the detoxifying enzymes, two studies found that cases with SHS exposure history were more than twice as likely to be deficient in GSTM1 activity, reaching an over sixfold excess risk in those exposed to 55 pack-years of SHS (produced by an active smoker, within a confined space such as home or office).^{150,151} Because 30 to 50% of the population carries the deficient or null GSTM1 genotype, such an effect modifier could be an important contributor to LCINS.¹⁴⁹⁻¹⁵¹ For another detoxifying enzyme N-acetyl transferase 2 (NAT2), a typical gene–environmental interaction with opposite directions between two genotypes has been reported: the *slow* acetylator genotype may confer an increased risk of LCINS; whereas, the *rapid* acetylator genotype may produce a steeper risk gradient among smokers with increasing pack-year doses.¹⁵¹

DNA repair genes encoding x-ray cross-complementing group 1 (XRCC1) and xeroderma pigmentosum group D (XPD) are two major DNA repair proteins. Polymorphisms of these two genes have been associated with altered DNA repair capacity and lung cancer risk. The adjusted ORs of XRCC1 Arg399Gln polymorphism (Gln/Gln vs Arg/Arg) was 1.3, but for never smokers, the adjusted OR was 2.4.^{152,153} XPD Arg156Arg polymorphism was associated with increased risk for lung cancer (OR = 2.5; *p* 0.03) adenocarcinoma of the lung (OR = and = 5.6; *p* 0.005) never smokers only.¹⁵⁴ The association= among of exon 5 polymorphisms in the *AGT* (O(6)-alkylguanine DNA alkyltransferase) gene and lung cancer risk was assessed in never smokers exposed to SHS by determining the frequencies of the Gly(160)Arg, Ile(143)Val, and Lys(178)Arg variant alleles. Never smoking individuals with the codon (143)Val and (178)Arg variant alleles were at 2.7-fold increased risk of developing lung adenocarcinoma.¹⁵⁵

Polymorphisms in genes involved in the inflammatory response and interaction with nonsteroidal antiinflammatory drug (NSAID) use in relation to lung cancer risk have also been reported. The functional SNPs in interleukin (IL)-1B T-31C, IL6 G-174C, IL8 T-251A, IL10 C-592T, cytochrome C oxidase subunit II (COX2) C8473T, COX2 A-1195G, and peroxisome proliferator-activated receptor gamma (PPARG2) Pro(12)Ala were studied. Never smokers carrying the variant allele were at a five-fold higher lung cancer risk than those carrying the homozygous wild-type allele.¹⁵⁶ Olivo-Marston et al have hypothesized a positive association between childhood SHS exposure and lung cancer risk that would be modified by genetic polymorphisms in the mannose-binding lectin-2 (MBL2) gene resulting in well-known functional changes in innate immunity.¹⁵⁷ A functional MBL2 haplotype was found to be associated with high circulating levels of MBL, and increased MBL2 activity was associated with doubled lung cancer risk among individuals exposed to childhood SHS. The indicated high-risk haplotype corresponds to a known overactive complement pathway of the innate immune system.¹⁵⁷ Genetic polymorphisms in innate immunity genes may also hold a role in the genesis of lung cancer caused by polycyclic aromatic hydrocarbons (PAH)—containing coal smoke.¹⁵⁸ The inflammatory response induced by coal smoke components may promote lung tumor development. The gene regions arachidonate 12-lipoxygenase (ALOX) 12B/ALOX15B and kallikrein-related peptidase (KLK)2 were associated with increased lung cancer risk globally. In addition, there were positive interactions between KLK15 rs3745523 and smoky coal use and between Fc fragment of IgE, low affinity II (FCER2) rs7249320, and KLK2 rs2739476 (OR: 10.8; $p = 0.003$).¹⁵⁹

Asbestos exposure, manganese superoxide dismutase (MnSOD) genotype, and lung cancer risk has been investigated, with no conclusive evidence for never smokers.^{160,161} There has not been a study reporting genetic modifying effects on exposures to residential radon and indoor air pollutions.

In summary, research on LCINS may contribute to understanding lung cancer in general. Specifically, biological determinants and mechanisms of genetic predisposition to lung cancer may be more evident in never smokers exposed to SHS, radon, or other agents, similar to the individual susceptibility in smokers.

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