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Review Article

NEVER SMOKERS WITH LUNG CANCER: A REVIEW

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ABSTRACT

With declining trend in smoking habits, studies suggest that lung cancer among never smokers is on the rise. Lung cancer among never smokers(LCINS) ranks seventh in terms of cancer related mortality worldwide. An estimate of 25% of all lung cancers that occur is not attributable to smoking. The sharp rise in the number of cases of LCINS suggest that risk factors other than smoking must be present. LCINS is commonly encountered in female population of Asian origin and is largely adenocarcinoma in histology. Air pollution (indoor and outdoor), passive smoking, exposure to asbestos, hormonal factors and genetic factors are some of the suggested risk factors for LCINS. However, there is no dominant risk factors whose significance has been validated. Identification of mutations in EGFR, KRAS and translocation EML4-ALK, commonly seen in never smokers than smokers which respond better to targeted therapy with tyrosine kinase inhibitors. This review summarizes our understanding of this poorly understood unique disease.

Key words: Lung cancer, never smoker, adenocarcinoma

INTRODUCTION

Lung cancer is a devastating disease and is the major cause of cancer related mortality. More than 1.4 million deaths occur annually due to lung cancer worldwide, are caused by smoking[1]. Global statistics estimate that 15% of lung cancer occur in men and 53% of lung cancer in women are not attributable to smoking, overall accounting for 25% of all lung cancer cases worldwide[2, 3]. Although a small fraction of lung cancer deaths occurs among never smokers, yet they account for a huge disease burden. Lung cancer in never smokers(LCINS), if considered a separate entity, ranks as the seventh most common cause of cancer related mortality worldwide[4]. An estimated 10-25% of lung cancer occur in never smokers[5]. Never smokers have been estimated to constitute about 30-40% of all lung cancer patients in Asian countries.

CLINICO-PATHOLOGICAL FEATURES

For clinic-pathological reasons lung cancer has been divided into two broad categories of small cell lung cancer(SCLC) and non-small cell lung cancer(NSCLC). NSCLC is further classified as squamous cell lung cancer(SCC), adenocarcinoma and large cell lung cancer[6]. LINC is likely to occur in women who are of east-Asian origin and adenocarcinoma is the most frequently encountered histological type[7], whereas small-cell carcinoma is very rare in never-smokers. Contradictory set of data exist concerning the age at which LCINS is diagnosed. Some authors encountered patients in a significantly younger age group, while the others found it to be common in older age group. In a French study, carried out by Quoix et al found that LCINS was more common among the older age group[8], while a Japanese study carried out by Kawaguchi et al encountered in younger population[9].

RISK FACTORS FOR LCINS

The causal relationship between smoking and lung cancer is well established. Smoking increases the risk of lung cancer by 10-20-fold compared with never smokers[10]. Besides smoking, studies have identified several other factors that increases the risk of lung cancer viz., exposure to environmental tobacco smoke, occupational exposure to carcinogens, air pollution, exposure to radon, dietary factors, etc.

Environmental tobacco smoke(ETS):

ETS is a combination of smoke that is released from burning of tobacco product and smoke that is exhaled by the smoker. Inhalation of ETS is termed as involuntary or passive smoking. Approximately one-third of adults and 40% of children are exposed to second-hand smoke worldwide, which accounts for 1% of all-cause mortality[11]. This exposure is estimated to cause >21 000 lung cancer-related deaths annually[5]. Taylor et al, 2007, conducted a meta-analysis, the pooled RR for never-smoking women exposed to passive smoking from spouses was 1.27 (95% CI: 1.17-1.37). The RR for North America 1.15 (95% CI 1.03–1.28), Asia 1.31 (95% CI 1.16–1.48) and Europe 1.31 (1.24–1.52)[12]. In a meta-analysis, Megumi et al, found

statistically significant association between passive smoking and lung cancer in Japanese non-smokers, with an overall relative risk of 1.28 (95% CI: 1.10-1.48)[13]. The abundance of evidence, consistency of finding across continent and study type, dose–response relationship and biological plausibility, overwhelmingly support the existence of a causal relationship between passive smoking and lung cancer. Couraud et al found that there was no clear association between passive smoking and somatic profile in lifelong never-smoker lung cancer[14].

Air pollution:

Outdoor air pollution: Air pollution has been classified as a carcinogen on the basis of epidemiological studies of lung cancer. With increase in industrialization and increase in the number of vehicles plying on roads lead to decrease in air quality. Air pollution is currently the principal issue in the field of environmental health. Outdoor air pollution is responsible for 1.3 million deaths in urban areas worldwide and indoor air pollution is responsible for 2 million premature deaths in developing countries[15]. Outdoor air pollution caused approximately 870 000 (95% CI: 130 000-1500 000) premature mortalities in China in 2010[16]. Emission of smoke from vehicles is the main source of outdoor air pollution which consist of carbon monoxide, ozone, particulate matter, nitrogen dioxide, benzene 1,3-butadine, polycyclic aromatic hydrocarbons and metals. An experiment was performed in rats, in which they were exposed to air pollutants of Tokyo metropolitan area, the experiment revealed that there was an increase in PAH-DNA adducts in lungs, nasal mucosa and liver of the rats after exposure to urban air for 4 weeks. This indicates, the pollutants exert genotoxic effects not only on the respiratory system such as lungs and nasal mucosa, but also indirectly on organs such as liver[17]. The risk of lung cancer mortality or morbidity increases by 7.23 (95% CI: 1.48–13.31)/ 10 μg/m^3 increase in fine particles (PM2.5), 13.17(95% CI:5.57–21.30)/10 parts per billion (ppb) increase in nitrogen dioxide (NO2), 0.81(95% CI: 0.14–1.49)/10 ppb increase in nitrogen oxides (NOx), and 14.76(95%C I:1.04–.34)/10 ppb increase in sulfur dioxide (SO2). These positive associations remained when analysis was restricted to never-smokers and showed no difference by sex[18].

Indoor air pollution: Indoor air pollution has always been implicated as an important risk factor for LCINS, especially among women. Coal has always been the main source of energy for house-hold purposes. Burning of coal in a poorly ventilated room worsens the condition even further. In a report published by WHO in 2014, estimated that over 4 million premature deaths annually are attributable to burning of coal and wood. The constituents of indoor air pollutants are complex which include particulate matter, sulfur oxides, nitrogen oxides, carbon monoxide, polycyclic aromatic hydrocarbons, formaldehyde, and dioxins, are by products of incomplete combustion of coal, wood and biomass.[19]. IARC classified indoor air pollution from coal as a known human carcinogen (IARC Group 1), while indoor air pollution from biomass was classified as possible human carcinogen (IARC Group 2A).

Xuanwei county of Yunnan province, China, has the highest incidence of lung cancer. The mortality

rate from lung cancer in Xuanwei was 28.20/ 100 000 in 1973-1975, and in 2004-2005 the incidence rate rose to 83.28/ 100 000, which was higher than the average of entire Yunnan province and 2.96 times higher than that of China[20]. A peculiar characteristic of lung cancer in Xuanwei county is that females who never smoked are affected the most. Some authors attribute the incidence of lung cancer in the region to indoor air pollution caused by the use of bituminous coal for house hold purposes[21, 22], while some consider it to be familial in nature. Compared with non-solid fuel users, predominant coal and wood users are at increased risk of developing lung cancer, OR=1.65(95% CI 1.41-1.93), among non-smokers. Lung cancer was associated with coal use among never-smoking Asian women (OR = 5.41; 95% CI, 3.65–8.00); however, results for wood use among never smoking Western women were more ambiguous (OR = 1.15; 95% CI, 0.81–1.64)[23].

Exposure to cooking fumes that arise from frying at high temperature could be a potential risk factor for lung cancer, especially among women. Stir frying and deep frying of food is common worldwide, especially China. IARC has classified fumes from high temperature frying as a probable carcinogen to humans[24]. Cooking oil fumes induces DNA damage by accumulation of reactive oxygen species(ROS)[25]. Cooking oil fumes contain trans,trans-2,4-decadienal(tt-dde), has a genotoxic effect on DNA of the bronchial epithelial cells[26]. The OR of lung cancer was highest for deep-frying (2.56 per 10 dish-years) followed by that of frying (1.47), and stir-frying had the lowest OR (1.12) in non-smoking women[27]. Exposure to cooking oil fumes was associated with both adenocarcinoma and non-adenocarcinoma types of lung cancer[28].

Burning of incense sticks is a common religious practice in major part of the world, at the same time it contributes to indoor air pollution. In a study, MacLennan found an association between burning of incense stick and lung cancer in women who were never smokers[29]. In a hospital based study, in Hong Kong, a significant association with exposure to incense burning during festivals (OR = 2.95 95% CI: 1.10–7.87). Tang et al conducted a hospital-based case-control study in Singapore and observed a null association between daily incense or mosquito coil burning and lung cancer (OR =0.90; 95% CI: 0.71–1.14) among non-smoking Chinese women[30]. Ger et al found and inverse association between frequency of burning incense sticks and lung adenocarcinoma[31]. Findings to date on the association between incense use and lung cancer is inconclusive. Larger studies with detailed information on incense is needed.

Familial lung cancer:

Family history of lung cancer has been raising the possibility of inherited traits that may increase the risk of lung cancer among some individuals[32, 33]. There are data to support that individuals with inherited mutations in Rb[34] and p53[35] genes may develop lung cancer. Recently, three genome-wide association studies (GWAS) of lung cancer and subsequent pooled GWAS analyses identified inherited susceptibility variants on chromosome 15q25, 5p15, and 6p21[36]. Bailey-Wilson JE et al in a genome wide linkage analysis reported 6q23-25 was the major susceptibility locus influencing the risk of lung cancer[37]. Individuals with a first-degree relative with lung cancer had a 1.51-fold increase in the risk of lung cancer, after adjustment for smoking and other potential confounders (95% CI:1.39, 1.63). The association was strongest for those with a

family history in a sibling, after adjustment OR = 1.82(95% CI: 1.62-2.05). Never smokers showed a lower association with positive familial history of lung cancer OR = 1.25(95% CI: 1.03-1.52), slightly stronger for those with an affected sibling OR = 1.44(95% CI: 1.07-1.93), after adjustment[38]. The risk of lung cancer was higher in individuals with a family history of lung cancer or any other cancer. First-degree female relatives were at higher risk of developing lung cancer than first-degree male relatives who were never smokers[39].

Radon:

Radon(^{222}Rn) is a byproduct of decaying radium, thorium and uranium present in soil and bedrock. Radon permeates through soil under high pressure towards low or negative pressurized areas such as basement of homes and buildings. Heating of homes creates a pressure difference which causes radon to be actively drawn up through the foundations to accumulate within indoor environment[40, 41]. Although, the major route of exposure is through the respiratory tract, one can be exposed to radon via skin contact and drinking of water contaminated with radon. Indoor radon exposure is associated with 16% increase in risk of lung cancer per 100Bq/m^3[42]. Estimated global environmental burden of disease attributable to residential radon was 1 503 000(984 000-2 086 000) DALYs for both sexes in 1990. Never-smokers had higher population attributable risk percentage (21%) than ever smokers. In never smoking population, the estimated life-time risk ratio was 1.304(97.5% quantile), which was higher than ever smokers[43].

Asbestos:

Asbestos, commonly used as an insulating material, causes lung cancer was recognized in the early 1940s. Occupational exposure to asbestos in the absence of asbestosis increases the risk of lung cancer rate ratio by 3.6(95% CI, 1.7-7.6) among non-smokers. Smokers in the absence of asbestos exposure is associated with a lung cancer rate of 10.3%(95% CI, 8.8-12.2). Asbestos exposure (in the absence of asbestosis) and smoking in combination are associated with a lung cancer rate ratio of 14.4 (95% CI, 10.7–19.4)[44].

Hormonal factors:

Hormonal factors have been suggested to lead to an elevated risk of lung cancer in women. The role of estrogen as a proliferative stimulus in breast cancer is well established, its possible role in lung cancer has only more recently been studied. Estrogen appears to play a significant role in the development of lung cancer in women. There are evidences that exogenous and endogenous estrogen may play a crucial role in the development of lung cancer, especially among women[45]. Estrogen receptors are expressed in normal and lung cancer tissues, the expression is more in lung cancer tissues, particularly adenocarcinoma of the lung[46, 47]. In vivo and in vitro experiments, Guang Feng et al found that over-expressed estrogen receptor-β (ER β) can promote the development of NSCLC, while SiRNAs targeting ER β gene can inhibit the growth of NSCLC and induce apoptosis of these cells via mitochondrial depolarization and caspase-3 activation. This suggest

that ER β deactivation or down regulation may have a potential therapeutic utility for the management of lung cancer[48]. The OR of adenocarcinoma among women who smoked and use ERT was 32.4 (95% CI=15.9-665.3) and, among women who never smoked had a OR of 1.0 (95% CI=0.3-3.8). This observation of an increased risk of adenocarcinoma with the use of exogenous estrogen supports the hypothesis that exogenous estrogen plays an important role in etiology of lung cancer in women[49]. Jong-Myon and Eun Hee Kim[50], in adaptive meta-analysis of cohort studies did not find any statistically significant association between HRT and lung cancer risk in women.

Diet and alcohol:

Red meat and processed food: Red meat and processed food has been associated with a variety of cancers[51]. High temperature cooking and preservation produces mutagens from present in meat[52]. Sinha et al ,reported that consumption of overcooked red meat increased the risk of lung cancer in women[53]. Many epidemiologists believe that diet high in total fat, saturated fat, or cholesterol are associated with increased risk of lung cancer. Alavanja et al reported that consumption of red meat, was associated with an increased risk of lung cancer even after controlling for total fat, saturated fat, cholesterol, fruit, yellow-green vegetable consumption and smoking history[54].

Coffee: Coffee consumption has been for long associated with lung cancer. Some authors reported significant association between heavy coffee drinkers and lung cancer, which was caused by residual confounding due to smoking, no significant association was observed in never smokers[55-58]

Alcohol: Alcohol has been linked to many types of tumors, but its association with lung cancer is still uncertain and inconclusive[59]. In a pooled analysis, Gordon et al reported an inverse association for consumption of wine and liquor, but not for beer[4].

Glycemic index(GI) and glycemic load(GL):

GI and GL are associated with risk of some selected cancers[60]. GI is a measure of how quickly carbohydrates in food result in elevation of blood glucose after eating. Post-prandial elevation of glucose stimulates the secretion of insulin. The insulin receptors activate the signaling pathways that are mitogenic, suggesting that insulin may influence the risk of cancer through the effects of insulin like growth factor(IGF)[61]. In a study, among non-Hispanic whites, there was a significant association between GI and lung cancer. The association between GI and lung cancer was even more pronounced among never smokers OR= 2.25(95% CI, 1.42–3.57)[62]. In a study, among Taiwanese population, Chin-Hsiao Tseng reported that diabetes and not insulin, is associated with increased risk for lung cancer[62] [63].

Physical activity and body mass index(BMI):

World Health Organization defines physical activity as any bodily movement produced by skeletal muscles that require energy expenditure. Physical inactivity has been identified as the fourth leading risk factor for global mortality causing estimated 3.2 million deaths globally. Physical activity is known to reduce the risk of cardiovascular diseases, diabetes, colon cancer and breast cancer . Moderate or rigorous physical activity is also associated with risk reduction for lung cancer both in men and women. Women with moderate amount of physical activity had fewer chances of squamous cell carcinoma and men had fewer chances of small cell carcinoma[64]. The effect of physical activity may be profound for younger people and my differ inconsistently by pack-years of smoking[51, 65] BMI, a surrogate marker of obesity is directly linked not only with the development of various types of cancers. Fat tissue is involved in the production of estrogens in women, particularly after menopause. BMI is also associated with menstruations, and low BMI, as observed in eating disorders, is often accompanied by amenorrhea. The role of BMI has been rarely considered in previous studies on reproductive factors and lung cancer, yet a higher BMI has been reported to be associated with a reduced risk of lung cancer in current and former smokers[66]. Rauscher et al reported a positive association between BMI and lung cancer in never-smokers and former smokers[67]. Kabat, in his study mentioned that, after adjustment for pack-years of smoking and other covariates, there was some evidence for inverse associations in current smokers (hazard ratio for highest BMI quantile relative to the lowest = 0.63; 95% confidence interval = 0.48-0.83) and in former smokers (0.69; 0.39-1.23), whereas in never-smokers, BMI was positively associated with lung cancer (2.19; CI 1.00-4.80)[68].

Infections associated with increased risk of lung cancer:

Human Papilloma Virus(HPV) has been for long associated with cervical cancers[69], anal cancers[70], vulvo-vaginal[71] and penile cancers[72]. Its association with lung cancer has not been firmly established. The prevalence of HPV positive lung cancer in Taiwan(55%), India(5%), Iran(25%), Italy(21%), France(2%) and Latin America(28%)[73]. There are evidences that HPV-18 may play a vital role in the development and progression of lung cancer, both squamous cell carcinoma and adenocarcinoma[74, 75]. Zhaik et al reported HPV infection was associated with lung cancer (OR = 5.67,95% CI: 3.09–10.40, P < 0.001). Similar results were also observed in HPV16 and/or HPV18 (HPV16/18) infection analyses (OR = 6.02, 95% CI: 3.22–11.28, P < 0.001). HPV16/18 was significantly associated with lung squamous cell carcinoma (SCC) (OR = 9.78, 95% CI: 6.28–15.22, P < 0.001), while the pooled OR was3.69 in lung adenocarcinoma (95% CI: 0.99–13.71, P = 0.052)[76].

In a large cohort study, it was reported, the incidence of lung cancer was 11-fold higher in patients with tuberculosis. Tuberculosis is an independent predictor of risk of lung cancer, the risk is higher for male and elderly[77].

Risk factor	Estimated risk (95% CI)	Study population	Ref
			[12]
ETS	RR=1.27(1.17-1.33)	Women, never smoker(meta-analysis)	
Familial	OR=1.25(1.03-1.52)	Never smoker(meta-analysis)	[38]
Air pollution			
Increase of 10μg/m^3in PM2.5	RR=1.18(1.06-1.32)	Never smoker(meta-analysis)	[18]
Increase of 10ppb in NO2	RR=1.12(1.03-1.21)	Never smoker(meta-analysis)	[18]
Increase of 10ppb in SO2	RR=1.08(1.07-1.12)	Never smoker(meta-analysis)	[18]
Increase of 10ppb in NOx	RR=1.01(1.00-1.02)	Never smoker(meta-analysis)	[18]
Coal and wood burning	OR=1.65(1.41-1.93)	Never smoker (pooled analysis)	[23]
Residential radon	Rate ratio=1.304(97.5 quantile)	Never smoker(meta-analysis)	[43]
Asbestos	RR=3.6(1.7-7.6)	Non-smoker(Cohort)	[44]
HRT	OR=1(0.3-3.8)	Women, never smoker(meta-analysis)	[49]
High GI	OR=2.25(1.42-3.57)	Case-control study	[62]
HPV infection		General population(meta-analysis)	[76]

Table 1: Risk factors of lung cancer and their estimated risk analyzed in this review

RR= Relative Risk, OR= Odds Ratio, HRT= Hormone Replacement Therapy, GI= Glycemic Index, HPV= Human Papilloma Virus

Opium:

In many countries of the world, particularly the countries in the Middle-East, recreational use of opium is quite popular. Opium has been associated with laryngeal, esophageal and bladder cancer[78, 79]. In a study conducted in Iranian population, after adjusting for the effect of ethnicity, education and pack years of smoking cigarettes, smoking opium remained as a significant independent risk factor with an OR of 3.1

(95%CI 1.2-8.1). In addition, concomitant heavy smoking of cigarettes and opium dramatically increased the risk of lung cancer to an OR of 35.0 (95% CI 11.4-107.9)[80]

GENETIC SUSCEPTIBILITY ASSOCIATED WITH LUNG CANCER IN NEVER-SMOKERS

The cumulative lifetime risk for lifelong smokers in their eighth decade of life is approximately 16% [81]. The host factors that confer protection from lung cancer in majority of the individuals who smoke and never develop lung cancer, or determine the susceptibility in those individuals who do not smoke and develop lung cancer is still not clear. It is widely accepted that genetic factors as well as epigenetic DNA changes contribute to the development of malignancy. Significant improvement has been achieved due to increased efforts to determine the molecular mechanism underlying tumorigenesis, which has led to the identification of multiple oncogenic alterations, including those observed in epidermal growth factor receptor (EGFR), Kirsten rat sarcoma viral oncogene homolog (KRAS), B-Raf proto-oncogene (BRAF), anaplastic lymphoma kinase (ALK). ROS proto-oncogene (ROS) and ret proto-oncogene (RET).

Epidermal growth factor receptor(EGFR):

The epidermal growth factor receptor (also known as ERBB) family is a subclass of receptor tyrosine kinase superfamily. The EGFR gene is located in chromosome 7p12, and consist of four members, EGFR (HER 1), ERBB2, ERBB3 and ERBB4. EGFR regulates multiple cellular functions, such as proliferation, survival, apoptosis, angiogenesis and cell differentiation[82, 83]. She-Juan Ann et. al., analyzed the relationship between driver genes and smoking status in 1800 Chinese population, and found EGFR mutation rates were higher in non-smokers than smokers 40.9% vs. 12.4% = 50.791, P,0.0005,[84]. The overall pooled prevalence for *EGFR* mutations was 32.3% (95% CI 30.9% to 33.7%), ranging from 38.4% (95% CI: 36.5% to 40.3%) in China to 14.1% (95% CI: 12.7% to 15.5%) in Europe. The pooled prevalence of *EGFR* mutation was higher in females (females vs. males: 43.7% vs. 24.0%; OR: 2.7, 95% CI: 2.5 to 2.9), non-smokers (non-smokers vs. past or current smokers: 49.3% vs. 21.5%; OR: 3.7, 95% CI: 3.4 to 4.0), and patients with adenocarcinoma (adenocarcinoma vs. non-adenocarcinoma: 38.0% vs. 11.7%; OR: 4.1, 95% CI: 3.6 to 4.8)[85]. In a study, Marchetti et al reported similar results[86]. The most frequently detected activating mutations in adenocarcinoma were exon 19 deletion followed by L858R point mutation in exon 21 and L861Q point mutation in exon 21[87]. Exon 19 deletion was also frequently encountered in patients with old pulmonary tuberculosis than patients without TB. Patients with old TB lesions who had EGFR mutations or exon 19 deletion survived longer than those who did not[88].

Echinoderm microtubule-associated protein like 4/anaplastic lymphoma kinase(EML4-ALK):

EML4-ALK is an important driver gene associated with adenocarcinoma of the lung in non-smokers.

EML4-ALK translocation is the most common ALK gene rearrangement. ALK is a transmembrane receptor with tyrosine kinase activities belonging to insulin growth factor superfamily, which is encoded on chromosome 2. The various fusion partners of ALK mediate ligand-independent dimerization of ALK, resulting in consecutive kinase activity, and thus transmits anti-apoptotic and cell proliferation signals via KRAS and PI3K pathways. Aberrant activation of ALK contributes to lung carcinogenesis after being fused with a number of other gene partners, most frequently EML4 gene, which is located on chromosome 2 and is reversely oriented with ALK[89]. The products of these translocations are fusion proteins with constitutively activated ALK tyrosine kinase, which plays a role in carcinogenesis by the aberrant phosphorylation of multiple intracellular substrates downstream of ALK-chimerical oncoproteins[90]. ALK rearrangement constitutes of 3%-5% of all NSCLC. Like EGFR mutation, EML4-ALK is commonly seen in adenocarcinoma and never-smokers. According to the predominance subtypes in adenocarcinomas, EML4-ALK positive lung cancers (54.5%) were sub classified as acinar adenocarcinomas (P=0.000044). Patients with EML4-ALK lung cancer were young (56 vs 64 years for other tumor types, P=0.0062)[91]. In a meta-analysis, Wang Ying et al, reported a significant lower EML4-ALK fusion rate was associated with smokers (pooled OR = 0.40, 95% CI = 0.30–0.54, P,0.00001), a significantly higher EML4-ALK fusion rate was associated with never smokers or light smokers. A significantly higher EML4-ALK fusion rate was associated adenocarcinomas (pooled OR = 2.53, 95% CI = 1.66–3.86, P=0.0001) and female (pooled OR = 0.61, 95% CI = 0.41–0.90, P = 0.01). A significantly lower EML4-ALK fusion rate was associated with EGFR mutation (pooled OR = 0.07, 95% CI = 0.03–0.19, P=0.00001)[91]. Fengzhi Zhao et al, reported similar result and also reported that EML4-ALK fusion was mutually exclusive of EGFR and KRAS mutation[92].

Kirsten rat sarcoma(KRAS):

KRAS along with HRAS and NRAS belong to the RAS gene family. The RAS gene family is activated by point mutation at codons 12, 13 or 61, in 20-30% of lung adenocarcinomas and 15-20% of all NSCLCs. Mutations in KRAS account for approximately 90% of RAS mutations in lung adenocarcinomas with 85% of the KRAS mutations affecting codon 12[93]. . In a study, 358 Chinese patients who were never-smokers with NSCLC, the frequency of KRAS mutation was 7.1% in male and 2.6% in females[94]. The frequency of KRAS mutation in more frequent in whites than Asian population, and most of them are current or former smokers[95]. KRAS mutation in never- smokers was most likely to be transition mutation(G→A), transversion mutation (G→T or G→C) was likely to be encountered in former or current smokers with adenocarcinoma[96].

In addition to EGFR, KRAS, and ALK mutations, other driver mutations have been discovered, such as BRAF, PIK3CA, NRAS, AKT1, MET, MEK1, and ROS1. Each of these mutations occur in less than 3% of lung adenocarcinomas. The great majority of the driver mutations are mutually exclusive and there is ongoing clinical research for their specific inhibitors.

PROGNOSIS OF LCINS

Overall prognosis of lung cancer patients is still unsatisfactory, with 5-year survival rate <15%[97]. More than 50% of women with lung cancer are not attributable to smoking. It is frequently seen in east-Asians and is adenocarcinoma in histology. Surgery is the treatment of choice if the tumor is detected in its early stage; if detected in the advanced stage chemotherapy and tyrosine kinase inhibitor(TKI) are the mainstay of treatment. The presence in the tumor of a mutation of the EGFR gene is a strong predictor of a better outcome if treated with tyrosine kinase inhibitor than conventional platinum doublet. Patients with lung cancer who are Asian, never smokers, non-smokers or light smokers and harboring EGFR mutations have longer progression free survival if they are treated with TKI than if they are treated with platinum based chemotherapy[98, 99]. Never smokers respond better to chemotherapy as well. Never smoking status as well as female gender, younger age, better PS, adenocarcinoma histology is a significant favorable prognostic factor [9].

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