It is estimated that one third of the world's adult population, and around 1.1 billion individuals, smokes tobacco, which makes every sixth human being a smoker. Smoking-related illness is estimated to cause ~ 5 million deaths per annum around the globe, but is considered a leading preventable cause of death. In developed countries, the rates of smoking have either leveled off or declined, but smoking-related deaths are on the rise in developing countries and are most common among the least-educated people. Initially, cigarette smoking prevalence was higher in males, but since the 1980s the gender gap has narrowed and plateaued. In 2003, in a school-based cross-sectional survey on water pipe-based tobacco smoking (sheesha) in Oman, 1,962 students were interviewed (26.6% were ever-smokers and 9.6% were current smokers). Among the current smokers, 15.5% were males and only 2.6% were females. In the USA in 2009, approximately 20.6% of adults and nearly 20% of high school students were cigarette smokers. An estimated 9% of them were smokeless tobacco consumers. Smokeless tobacco products include products such as moist snuff, chewing tobacco, snus (moist powdered tobacco) and dissolvable nicotine products such as strips and sticks. Current evidence, however, does not support the opinion that the use of these products is safer than smoking. Additionally, there is substantial evidence that these products can be implicated in oral and pancreatic cancers, precancerous oral lesions, gingival recession, gingival bone loss around the teeth, tooth-staining, and nicotine addiction.

In the USA, tobacco use is responsible for nearly 1 in 5 deaths. In 2012, the estimated percentage of new lung cancers in males (116,470 cases) and females (109,690 cases) was 14% each. Among these
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Tobacco is processed from the leaves of plants in the genus *Nicotiana*. Besides its use as a drug, the tobacco plant is also used in bioengineering and as an ornamental plant. For many developed as well as developing countries, it remains a valuable cash crop.

*Nicotiana tabacum* and *rustica* are considered the main commercial species, with alkaloid nicotine as the addictive constituent of tobacco responsible for its tolerance and dependence; however, it is not a carcinogen. After harvest, tobacco is cured over many days, allowing slow oxidation and degradation of the constituent carotenoids. This allows for the ‘smoothness’ of the smoke, giving cured tobacco its aromatic flavours.

After curing, tobacco is moved to a storage area for processing. For the intact plants, the leaves are removed from the tobacco stalks in a process called stripping, which makes the smoke milder and more inhalable. Tobacco is subsequently packed into various forms for consumption (i.e. smoking, chewing, snuffing, etc.) It is the cured tobacco which is easily inhalable and causes lung cancer and other disease processes.

*Patient Characteristics, Environmental Factors, and Lung Cancer*

Certain patient characteristics have consistently shown an impact on lung cancer outcomes. For example, lung cancer is a disease of the elderly, although advancing age was not a prognostic factor for survival but high scores on the Charlson Comorbidity Index (CCI) were a factor. Taken together, toxicity, age and high CCI scores were significant predictors. The incidence of lung cancer is higher among men (34%) as compared to women (13.5%). The age-standardised ratio for cancer incidence is 33.81%, and for mortality is 29.2% in men alone.

In the past, the incidence was lower in females, but worldwide it is now the fourth most frequent
cancer in women (516,000 cases; 8.5% of all cancers) and the second most common cause of cancer deaths (427,000 deaths; 12.8% of the total). The highest incidence rate in women is observed in North America, where lung cancer is now the second most frequent cancer in women. This is attributed to smoking. It is the lowest in central Africa, where it is the 15th most frequent cancer in women. As one in 5 women who develop lung cancer is a never-smoker, it remains a mystery as to what exactly causes their cancer.

Lung cancer in never-smokers is proposed to be due to multiple risk factors, including genetic predisposition—although this is exceedingly rare (1% with >3 affected relatives). Genetics mutations remain an underlying cause as we do encounter lung cancer at a relatively earlier age when it runs in families. Among the first studies revealing a genetic link was one conducted over 40 years ago by Tokuhata et al. The study revealed that never-smokers with lung cancer were 40% more likely than never-smoking controls to report a first degree relative with lung cancer. Women were more likely to report such a family history and 10–15% had at least one first-degree relative with the disease.

In a landmark hormonal therapy study of 16,608 post-menopausal females, the risk of developing non-small-cell lung cancer (NSCLC) was not significant (P = 0.21) in the experimental arm (treatment with oestrogen/medroxyprogesterone acetate) compared to the placebo group; however, after a follow-up of 5 years a divergence emerged, with more lung cancer diagnoses in the treatment arm. In addition, these females had poorly-differentiated tumours and a higher incidence of metastatic disease. There was a 30% increase in cardiovascular events, a 26% increase in breast cancer, and a 40% increase in cerebral vascular accidents (CVAs) compared to the placebo group. The hormonal treatment of postmenopausal women did not increase incidence of lung cancer, yet, it increased the lung cancer specific mortality, in particular deaths from NSCLC.

Passive, or second-hand smoke from a spouse, friends, roommates, or childhood exposure from parents; vehicle or factory exhausts; cooking fumes in poorly ventilated kitchens; residence in mountainous areas (radon A, B, and C exposure), and occupational exposure or environmental toxins (asbestos and arsenic), have all been implicated in lung carcinogenesis.

Certain occupations are also associated with a higher risk of developing lung cancer (e.g. miners, asbestos workers, glass manufacturers, painters, printers and masonry workers). Many occupational substances carry a substantial risk, e.g. diesel and welding fumes, motor exhaust, natural fibres (asbestos, silica, wood, or coal dust), radon, reactive chemicals (mustard gas, vinyl chloride) and solvents (benzene, toluene). Adenocarcinoma subtypes are also associated with subpleural scars secondary to chronic inflammation (e.g. old infarcts, healed granuloma or pneumonitis and post-traumatic scars). C-reactive protein (CRP) levels were documented to be higher in NSCLC in a study suggestive of an aetiologic role of chronic inflammation in NSCLC carcinogenesis.

Females with lung cancer tend to live longer compared to men because of diagnosis at a younger age, possibly diagnosis at an earlier stage, having adenocarcinoma more frequently, and perhaps due to inherent longevity. It is also possible that their superior survival in lung cancer is due to differences in nicotine metabolism, cytochrome P-450 enzymes and lifestyle.

Tobacco Metabolism

Tobacco carcinogens are metabolised by cytochrome P-450 enzymes to make them readily excretable. Lipoxygenase, cyclooxygenase, myeloperoxidases, and monoamine oxidases may also be involved, although infrequently. The oxygenated intermediate metabolites undergo subsequent transformations (detoxification and secretion) by glutathiones, sulfatases, or uridine-5′-diphosphate-glucuronosyltransferases (U5′DPGT). A few of the metabolites generated during these processes react with the deoxyribonucleic acid (DNA) to form covalent binding products called DNA adducts in a process called metabolic activation. Carcinogens like polycyclic aromatic hydrocarbons (PAH) and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) require metabolic activation to exert their carcinogenic effects. The carcinogenic metabolites of PAH-benzopyrenes (i.e. 7,8 diol 9,10 epoxides) and nicotine-derived nitratosamine ketone (NNK or NNAL) react with DNA to form adducts. Alpha-hydroxylase converts methyl adducts from
Weight loss results from the release of cytokines (IL-6, IL-1β, interleukin-1RN, and tumour necrosis factor) with the contribution of anorexia, nausea, vomiting, diarrhoea, mediastinal lymphadenopathy compromising food passages, cytotoxic therapy and concurrent illness. The severity or burden of comorbidity has also been reported to have a clear relationship with poor survival in a variety of cancers, including lung cancer.

Poor patient performance status (PS) is also associated with poorer survival outcomes. The absolute benefit of chemotherapy in metastatic disease at one year varied according to the PS. In PS 0 and 1, the absolute benefit was 8%. In PS 2, the benefit was 5%, while in PS 3 it was 4%. Median survival fell inversely with increasing PS in the Eastern Cooperative Oncology Group (ECOG) E1549 trial [Table 1].

Race is also prognostic with lung cancer risk varying between different races and ethnicities. In the USA, age-adjusted Surveillance, Epidemiology and End Results (SEER) incidence rates for lung cancer in Afro-Americans and Caucasians are higher compared to Alaskans, Indians, Asians, Pacific Islanders and Hispanics. Weight loss (hazard ratio [HR] 0.87; \( P < 0.001 \)) is considered to be associated with poorer survival. In the E1594 trial, patients without weight loss (<10%) had superior survival. Weight loss results from the release of cytokines (IL-6, IL-1β, interleukin-1RN, and tumour necrosis factor) with the contribution of anorexia, nausea, vomiting, diarrhoea, mediastinal lymphadenopathy compromising food passages, cytotoxic therapy and concurrent illness. The severity or burden of comorbidity has also been reported to have a clear relationship with poor survival in a variety of cancers, including lung cancer.

### Table 1: Survival difference by performance status and degree of weight loss in the E1594 trial

<table>
<thead>
<tr>
<th>ECOG PS</th>
<th>Median Survival</th>
<th>Weight Loss</th>
<th>Median Survival</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>10.8 m</td>
<td>Nil</td>
<td>9.5 m</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>7.1 m</td>
<td>&gt;10%</td>
<td>4.9 m</td>
<td>0.0001</td>
</tr>
<tr>
<td>2</td>
<td>3.9 m</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ECOG = Eastern Cooperative Oncology Group; PS = performance status.
Approximately 20 potential carcinogens of ~3,500 chemicals have been detected in burning cigarette. The most established are the polycyclic aromatic hydrocarbons (PAH) like benzo(a) pyrenes, and the tobacco-specific N-nitrosamine 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), while others include Asz-arenes, Dibenz(a,h)acridine, inorganic compounds like cadmium, chromium, nickel, arsenic, radioactive polonium (Po210) and organic compounds like butadiene.32 Nitrates in the tobacco are reduced to NH2 and NH3 while smoking. Air-cured tobacco contains higher concentrations of aromatic amines as compared to flue-cured tobaccos (e.g. the urinary bladder carcinogens β2-naphthylamine and 4-aminobiphenyl).34

Cigarette smoke contains high levels of acrolein, which is toxic to the ciliated lining of the lungs, and other agents such as nitrogen oxides, acetaldehyde, phenols, and formaldehyde, which may contribute indirectly to pulmonary carcinogenicity in animals and humans.35

Cigarette smoke also contains free radicals (FR) (e.g. hydrogen peroxide [H2O2], hydroxyl ion [OH–], sulfoxide anion) which induce oxidative damage in animal models as well as humans, while catechol and hydroquinone play their roles in single strand DNA breaks caused by the release of FR.34 However, the evidence for the latter remains relatively low due to negative trials of anti-oxidant therapy in humans. Total NNAL and cotinine (nicotine metabolite) were measured in urine from smokers. The highest tertiles exhibited an 8.5-fold increased risk for lung cancer relative to those smokers with a comparable smoking history but possessing the lowest tertiles of these metabolites. These findings directly link NNK exposure to lung cancers in humans.36

Smoking has multidimensional effects on lung cancer [Figure 3]. Tobacco smoking remains the most consistent causative agent in lung carcinogenesis in animal and human models, yet, over the past decade or so, it has also emerged as a prognostic and predictive clinical characteristic.

**Proto-oncogenes, Oncogenes, and Cellular Pathways in Malignant Transformation**

Malignant transformation involves certain genetic and epigenetic changes such as hypomethylation, and methylation of the cytosine guanine promoter region (CpG) leading to the silencing of tumour suppressor genes. Generally, hereditary genetic defects lead to the relatively early onset of cancers.

**Table 2: Prevalence of subtypes of lung carcinoma in smokers and never-smokers**

<table>
<thead>
<tr>
<th>Histologic Subtype</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Smokers</td>
</tr>
<tr>
<td>SCC</td>
<td>42</td>
</tr>
<tr>
<td>Adenocarcinoma (includes NOS &amp; BAC)</td>
<td>39</td>
</tr>
<tr>
<td>Carcinoids</td>
<td>07</td>
</tr>
<tr>
<td>Others</td>
<td>08</td>
</tr>
</tbody>
</table>

Prevalence of subtypes of lung cancer in smokers and never-smokers (52 patients) at SQUH

| SCC                | 91      | 9              |
| Adenocarcinoma     | 61      | 39             |
| Undifferentiated CA| 33      | -              |
| SCLC               | 66.7    | 33.3           |

Source: Hecht SS. Tobacco carcinogens, their biomarkers and tobacco induced cancer.34

SCC = squamous-cell carcinoma; NOS = not otherwise specified; BAC = bronchioalveolar carcinoma; SQUH = Sultan Qaboos University Hospital; CA = cancer; SCLC = small-cell lung carcinoma.
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4-anaplastic lymphoma kinase fusion gene [EML4 ALK] in lung cancer.38 Proto-oncogenes are turned off once the embryogenesis and developmental processes they regulate are completed. However, in cancer, proto-oncogene activity remains high, or is inappropriately reactivated later in life.

In order to grow and divide, cells respond to outside signals through the binding of extracellular ligands (growth factors) to the extracellular region of certain trans-membrane receptors, such as EGFR. When a ligand binds to a cell receptor, the receptor will frequently undergo a transformational change in its shape, which in turn leads to activation of tyrosine kinase (TK) activity in the intracellular domain and propagates the cell signal transduction pathways which regulate cell growth, proliferation, angiogenesis, apoptosis or cell death.40 In cancer, these processes may become autonomous due to overexpression of these receptors by virtue of the genetic defects mentioned above.

Molecular Signalling Pathways in Tobacco Smokers and Never-Smokers

**CELL PATHWAY ACTIVATION IN SMOKERS—THE SMOKES PATHWAYS**

Smokers have their own set of driver mutations which are distinct from lung cancer in never-smokers.41 Common mutations in smokers include p53 (>50%), K-Ras (~30%), p16 (>70%), STK11 (11%), and others like F-HIT and T790M. In contrast, the incidence of EGFR (4%) and EML4 ALK mutations (2%) are relatively low in smokers with lung cancer. Some of these are successfully targeted while others are being explored as targets for new agents [Table 3].42

Figure 3: Impact of tobacco smoke on lung cancer. GA = general anaesthesia; Adenoca = adenocarcinoma; SCC = squamous-cell carcinoma; TKI = tyrosine kinase inhibitor; QoL = quality of life; CA = cancer; EGFR,Mut = epidermal growth factor mutation; K-Ras,Mut = Kirsten rat sarcoma viral oncogene homolog mutation; EML4 ALK = echinoderm microtubule-associated protein like 4-anaplastic lymphoma kinase fusion.
The p53 gene is a tumour suppressor gene which controls the apoptotic pathways and keeps a check and balance on cellular proliferation and death. The mutation occurs in a variety of human cancers, including lung cancer (>50%). Point mutations at guanine are common. In a sample of 550 p53 mutations in lung tumours, 33% were guanine (G)→thymine (T) transversions, while 26% were G→adenine (A) transitions. p53 mutations show a dose-dependent increase in G→T transversions at hotspots frequently after exposure to tobacco carcinogens. Lung cancers have a lot of overlap between the mutation spectrum of p53 in smokers and never-smokers. As a result, p53 genotyping cannot be used to preclude different tumours solely on its basis. A trial at the Massachusetts General Hospital investigated the p53 gene in surgically-removed lung cancers, and found 29% of patients (n = 85) harbouring p53 mutations. The patients with p53 mutations who were current smokers were significantly older and had smoked for significantly more years (P <0.01) than those without p53 changes. A large number (40%) of G→cytosine (C) to T→A transition mutations were observed due to increasing cumulative exposure to smoke. Interestingly, p53 mutations were also seen in patients with a history of occupational exposure to asbestos—5% for patients without versus 20% with exposure (P <0.05).

Genes in the wide Ras gene superfamily, including H-Ras, N-Ras, and K-Ras oncogenes, on chromosome 12p12.1 encodes a family of membrane-localised GTP-binding proteins that function for TK activation and subsequent downstream cell signal transduction in regulating cell growth, differentiation, and apoptosis. The Ras proteins interact with multiple effectors through the MAPK/STAT/PI3K signalling cascades. Wild-type K-Ras has intrinsic GTPase activity, which catalyses the hydrolysis of bound GTP to GDP thereby inactivating the Ras growth-promoting signal, whereas oncogenic K-Ras is locked into the GTP-bound state, leading to constitutive Ras signalling. Mutations in K-Ras occurred in ~43% of NSCLC cases in one study. It is common in mucinous adenocarcinoma, in elderly patients who are heavy smokers, and in earlier stages and grades, but not in large-cell lung cancers or bronchioloalveolar carcinoma (BAC). However, its frequency falls with stage and grade progression. The occurrence in never-smokers is low (~15%) and is more likely to be transition mutations. In contrast, the majority of mutations from tobacco smoke exposure occur in codons 12 (G→T transversion) and 13.

A trial on Asian patients revealed that K-Ras...
mutations were associated with ever-smoking status, male gender, and poor differentiation; however, Western studies have not been able to validate these findings. In the National Cancer Institute of Canada (NCIC) BR.21 study, 28% of 731 patients had a K-Ras (wild) genotype that responded well to tyrosine kinase inhibitors (TKIs) while 15% had mutations that conferred primary resistance to targeted therapy.

Data from the TRIBUTE trial reveals that EGFR and K-Ras mutations rarely occur together, and that survival was inferior in the group of patients with the K-Ras mutation who were treated with the addition of TKIs to chemotherapy. The presence of a K-Ras mutation rules out an EGFR mutation, and is also a marker of TKI inactivity. Patients harbouring the K-Ras mutation are best treated with chemotherapy. In a recent trial, MEK 1 and 2 inhibitors (selumetinib), which are downstream of K-Ras, were given in combination with docetaxel and compared to docetaxel alone. The combination with the new agent enhanced response rates (RR) and progression-free survival (PFS), but overall survival (OS) remained only numerically superior in patients harbouring the K-Ras mutation.

LKB1/STK11 (encodes a serine-threonine kinase) is a tumour suppressor which negatively regulates mammalian target of rapamycin (mTOR) signalling. It is inactivated in 5–15% of primary lung adenocarcinomas. Homozygous deletion or loss of heterozygosity (LOH) of chromosome 19p at the LKB1 locus occurred in 90% of the tested specimen in primary lung cancers. The mutation is more frequent in lung cancers in smokers than never-smokers (P 0.007), and commonly occurs with K-Ras mutations (P 0.042) but infrequently with EGFR mutations (P 0.002). T790M (substitution of methionine for threonine at aa position 790) in tumours that progress on TKIs are more common in smokers and ex-smokers than in never-smokers. This accounts for 50% of acquired resistance to TKIs. Afatinib (irreversible TKI) has been approved as a targeted therapy against T790M.

The p16 tumour suppressor gene is inactivated in >70% of human NSCLC via homozygous deletion or aberrant hypermethylation of the promoter region. Smoke carcinogens may also cause LOH and chromosomal deletions in the F-HIT gene. The downregulation of SIRT1 activity has also been found to be confined to lung tumours in smokers, whereas it remains upregulated in normal bronchial epithelial cells from active smokers. There is substantial evidence that cigarette tar and nitric oxide (NO) act synergistically to cause single strand DNA breaks. The lower incidence rates of the EGFR mutation and EML4 ALK mean that a smoker cannot undergo equally effective and possibly less toxic oral-targeted therapies.

Cell Signalling Pathway Activation in Never-Smokers

More than 20,000 people who do not smoke tobacco eventually develop lung cancer in the US each year. Cancer in never-smokers follows different cell signal transduction pathways, including EGFR mutations in 37% (exon 21 L858R or exon 19) enabling targeted therapy; p53 mutations in 26%; human epidermal growth factor receptor 2 (HER2/neu) in 2%; over-expression and activation, or a higher frequency for EML4 ALK fusion in 12%; enabling oral crizotinib (targeted) therapy through other unknown mutations. Never-smokers with higher EGFR frequency and gene copy numbers do well with TKI therapy, where it has shown to be associated with improvement in RR and PFS. There is a lower frequency of p53 G→C to T→A mutations, and lower frequency of mutations at hot spots. As described earlier, never-smokers have a lower frequency of K-Ras mutation (~15%), the majority of which are transition mutations with a lower frequency of K-Ras transversions, and low serine/threonine kinase 11 (STK11) mutations (also known as liver kinase [LBK1] mutations).

In a trial from East Asia of 152 never-smoking NSCLC patients, 75% harboured EGFR mutations, 6% had HER2 mutations, 5% had EML4 ALK fusions, 2% had K-Ras mutations, 1% harboured ROS1 fusions, 0% had b RAF mutations, and 10.9% had unknown mutations. The odds of an EGFR mutation are 6.5 times higher in never-smokers (P <0.0001), 4.4 times higher in those with adenocarcinoma (P <0.0001), 1.7 times higher for females (P 0.039), and 4–6 times higher in East Asians. Advanced age and acinar predominant subtypes were also independent predictors of EGFR mutations.
Impact of Tobacco Smoking on Lung Cancer Outcomes

Smokers are prone to frequent side-effects during therapeutic courses of chemotherapy and radiotherapy (i.e. mucositis), and while under general anaesthesia (GA), and to surgical complications. Their post-surgical survival is also poorer. The 10-year overall and disease-specific survival rate falls as the number of cigarette packs smoked increases in patients with surgically-resected, Stage I NSCLC. Multivariate analysis from a retrospective study in Singapore, however, could not find a significant correlation between smoking and survival. Smoking is also associated with poorer quality of life and predisposes patients to secondary cancers and chronic lung diseases, potentially making these patients unsuitable for or vulnerable to subsequent oncological interventions.

EGFR Mutations in Lung Cancer in Smokers

In a relatively older trial, most patients harbouring the EGFR mutation had adenocarcinomas and had smoked <100 cigarettes in his or her lifetime (never-smokers). Seven of the 15 adenocarcinomas resected from untreated never-smokers harboured the mutations, in contrast to 4 of 81 NSCLCs resected from untreated former or current smokers (P = 0.0001). In 2004, Lynch et al. initially described 9 patients with excellent responses to gefitinib, of whom 6 were never-smokers. Cigarette-smoking history was used to estimate the likelihood of mutations in EGFR gene exons 19 and 21 in lung adenocarcinomas at the Memorial Sloan Kettering Cancer Center (MSKCC); the mutation was detected in 51% of 67 never-smokers, 19% of 151 former smokers and 4% of 47 current smokers. The number of packs smoked per year (more than 15 packs/year, P < 0.001) and smoke-free years (smoking cessation less than 25 years ago, P < 0.02) predicted the lower prevalence of EGFR mutations compared to smokers.

A Japanese trial examined EGFR gene mutations within exons 18–21 and their correlations to clinico-pathological factors and other genetic alterations in 154 resected tumour specimens. EGFR mutations were observed in 39%, all of which were adenocarcinomas. Among the patients with adenocarcinoma, EGFR mutations were more frequently observed in non-smokers than former or current smokers (83%, 50% and 15.2%, respectively); in women than men (76.3% versus 34.0%); in tumours with a bronchioalveolar component than those without (78.9% versus 42.9%), and in well- to moderately-differentiated tumours compared to their poorly differentiated counterparts (72%, 64.4% and 34.2%, respectively). Tumours with EGFR mutations had no K-Ras codon 12 mutations, which remains a known tobacco carcinogen-induced mutation.

Patients who smoke have a lower chance of having an EGFR mutation (14%) and the vast majority harbour wild-type EGFR, failing to qualify them for targeted TKI therapy, while current smokers who do harbour the mutations have poorer RR, PFS, and OS despite TKIs. However, all categories harbouring EGFR mutations benefit from the targeted TKIs, irrespective of their smoking status.

Tobacco Smoke—A Prognostic and Predictive Characteristic

In an exploratory subgroup analyses of a trial using salvage erlotinib (first or second line), OS was markedly increased in never-smokers (<20% of patients) on both univariate (P < 0.001) and multivariate (P = 0.048) analyses as compared to ex-smokers. In a retrospective review of 139 NSCLC patients at MSKCC, a multivariable analysis revealed that the presence of adenocarcinoma with any bronchioalveolar features (P = 0.004), and being a never-smoker (P = 0.006) were independent predictors of response. Retrospective analyses of IDEAL 1 and 2 studies reveal that never-smokers derive greater benefit from TKI therapy compared to ever-smokers. In a phase II Iressa Survival Evaluation in Lung Cancer (ISEL) study, a pre-planned subgroup analysis showed significantly longer survival in the gefitinib group than the placebo group for never-smokers (n = 375; median OS = 8.9 months versus 6.1 months; P = 0.012) in adenocarcinoma. A survival advantage for erlotinib compared with a placebo was demonstrated in the NCIC BR.21, a randomised, double-blind study of patients (n = 731) with...
advanced-stage NSCLC. A marginally significant interaction was observed between smoking history and treatment (P = 0.054). The hazard ratios (HR) were 0.42 among never-smokers and 0.87 for smokers, indicating that erlotinib was beneficial irrespective of the smoking status, but the TKI was more useful in never-smokers. Patients with EGFR-positive tumours who had never smoked derived the greatest survival benefit from erlotinib relative to a placebo (HR 0.28; P = 0.0007).23

In an unselected NSCLC population in the TALENT and INTACT 1 and 2 studies, there was no benefit when erlotinib was combined concurrently with chemotherapy when compared to chemotherapy alone. It should be noted, however, that the endpoints of these studies were not meant for evaluating variables like smoking status.746566

However, in the TRIBUTE trial, the addition of erlotinib to chemotherapy when compared to chemotherapy plus a placebo did reveal a doubling in survival in 10% of the never-smokers of the subgroups. When compared with former or current smokers, the never-smokers were relatively younger, predominantly female, and frequently harboured adenocarcinoma. While the median OS of never-smokers on a placebo was similar to that of current or former smokers on a placebo (~10 months), the never-smokers on erlotinib had a doubling of median survival (22.5 months), and an improved median time to progression (TTP) (6 versus 4.3 months).75

A trial by Mok et al. was carried out primarily on never-smokers (EGFR mutations in 61%) or on light ex-smokers (EGFR mutations in 47%). Their IPASS trial used oral gefitinib and compared it to paclitaxel carboplatin in East Asian chemo-naive, never- or light ex-smokers (n = 261). The RR was 71% with TKI and 43% with chemotherapy. The RR was 1% with TKI and halved with chemotherapy in wild-type EGFR. Patients with an EGFR mutation had a doubling in PFS with gefitinib, while in those having wild-type EGFR, the PFS almost tripled with chemotherapy.76 For never-smokers in the Caucasian EURTAC study, the median PFS was 9.7 months in favour of erlotinib as compared to 5.1 months with chemotherapy.77

In a review of 4 randomised trials of gefitinib as first-line therapy in advanced NSCLC, the majority of patients were women (63–88%) and had the adenocarcinoma subtype (90–100%). In the various patient subgroups, the range for never-smokers was 65.8–100% and the EGFR mutation status was known in 33–100%. Activating somatic mutations were found in a high percentage in this subgroup (49–100%), and there was a consequent superior efficacy with TKIs.78

Erlotinib was compared alone or with carboplatin paclitaxel in never- or light former-smokers and showed similar efficacy, but TKI was less toxic in predominantly Caucasian never-smokers with advanced NSCLC.79 In a Brazilian study comprising of NSCLC patients (n = 285), the majority were ever-smokers (76%). Among the never-smokers (n = 56), there were significantly more women (68%) and adenocarcinoma subtypes (70%). The OS at 5 years of never-smokers and ever-smokers were significantly different (P = 0.049). The median survival time was 14.9 months for ever-smokers and 22.1 months for never-smokers. Multivariate analysis of factors related to OS, using the Cox regression for never-smokers, was highly significant (HR 0.58; P = 0.047) without any influence of female gender or adenocarcinoma.80 In a subgroup analysis of the Chinese OPTIMAL trial, the P value for the interaction test between various smoking statuses was 0.34, favouring the TKI in never-smokers.

On the contrary, a recent trial from western Japan (WTOG 3405) could not validate the effects of smoking status, age, sex, postoperative recurrence and mutation type on OS on univariate or multivariate analyses while comparing gefitinib to cisplatin and docetaxel chemotherapy.81

A recently published trial of 1,725 patients, cisplatin and pemetrexed versus cisplatin and gemcitabine showed an interesting result among enrolled never-smokers who comprised 14–15% of the overall patient population. This trial showed that never-smokers had a superior median OS in both chemotherapy arms compared to current or former smokers (15.9 versus 10.0 months in the cisplatin and pemetrexed arm; 15.3 versus 10.3 months for the cisplatin and gemcitabine arm).82

The superior survival in the preceding trials, are attributable to higher EGFR mutation rates in never-smokers. Therefore, tobacco smoking has indirectly emerged as a good predictor for response to TKI and is generally associated with enhanced survival outcomes.
**Conclusion**

Smoking has a multidimensional impact on lung cancer. It remains the most consistent causative agent for developing the disease and carries a definitive prognostic and predictive value. Adenocarcinoma is more common in never-smokers and females. The rates for EGFR and EML4 ALK mutations are higher in never-smokers providing these individuals a chance for targeted therapy. However, TKIs are ineffective in smokers with K-Ras mutations. Therapy optimisations should be integral while planning therapy. There is enormous room for molecular profiling of never-smokers where carcinogenesis stays presumptive. Smoking during a course of therapy remains detrimental, and patients should be advised to discontinue it as soon as possible. Strict regulations to control tobacco smoking can avert a number of human deaths globally, and lung cancer particularly. The fight between health authorities, the tobacco industry, and smokers continues to haunt humanity while the tobacco industry continues to pocket millions of USD in profit.

**ACKNOWLEDGMENTS**

The author wishes to thank the following two students who helped with the literature search in epidemiology part of the review article: Zainab Al-Jabri and Hanan Al-Shamli.

**References**


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