# Lung Cancer in Never Smokers

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**Abstract** Lung cancer is predominantly associated with cigarette smoking; however, a substantial minority of patients with the disease have never smoked. In the US it is estimated there are 17,000–26,000 annual deaths from lung cancer in never smokers, which as a separate entity would be the seventh leading cause of cancer mortality. Controversy surrounds the question of whether or not the incidence of lung cancer in never-smokers is increasing, with more data to support this observation in Asia. There are several factors associated with an increased risk of developing lung cancer in never smokers including second hand smoke, indoor air pollution, occupational exposures, and genetic susceptibility among others. Adenocarcinoma is the most common histology of lung cancer in never smokers and in comparison to lung cancer in smokers appears less complex with a higher likelihood to have targetable driver mutations.

**Keywords** Non-smoker lung cancer • Lung cancer in nonsmokers

## Introduction

Lung cancer is strongly associated with cigarette smoking [1–3]; however, there is a substantial minority of patients who have never smoked. This population is more likely to have distinct molecular markers [4–7], but has less well established risk factors adding to the complexity in understanding this subset. The epidemiology, risk factors, molecular biology, treatment and prognosis of lung cancer will be discussed in never-smokers. Small cell lung cancer in never-smokers is incredibly rare with only case reports and series published; therefore, we will focus on non-small cell lung cancer (NSCLC) [8–11]. In addition, from this point forward a person who is a never smoker is identified as having smoked less than 100 cigarettes in a lifetime.

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## Epidemiology-Defining the Never Smoker Population

Lung cancer prior to the invention of mechanized cigarette making was a rare disease. What percentage of patients with the disease were never-smokers is unclear; however, inhaled tobacco was available on a limited basis [12, 13]. The capacity to identify never-smokers in numbers meaningful for global and regional analysis to date has been limited as several cancer registries have inconsistently identified smoking status. The studies that exist with data on never-smokers have often had to resort to creative ways of estimating smoking prevalence.

### *What Is the Incidence and Mortality of Lung Cancer in Never-Smokers?*

In 2012, there were an estimated 1.8 million new cases of lung cancer reported by GLOBOCAN [14]. In actuality the incidence varies dramatically by continent or region [15–18]. Given the high fatality rate of lung cancer, mortality closely tracks incidence with 1.59 million deaths projected globally for 2012 [14]. In the US the incidence of new lung cancer cases for 2014 is estimated at 224,210 and deaths estimated at 159,260 [19]. Reports in the US have estimated among never-smokers annual deaths of 17,000–26,000 from lung cancer that as a separate entity would be the seventh leading cause of cancer mortality [7, 20].

### *Is Incidence or Death Rate of Lung Cancer in Never Smokers Increasing? Is There a Difference by Sex or Ethnicity?*

There have been very few studies that have been able to accurately report incidence rates of lung cancer in never-smokers, in particular across regions. Sun et al. and Subramanian et al. report that in the year 2000 never-smokers were 25 % of all cases of lung cancers globally, of which 15 % were men and 53 % were women [6, 7]. These percentages, however, are actually the inverse of percentages taken from the Parkin et al. study of smoking related lung cancer [21]. In contrast, Wakelee et al. performed direct measurement of the incidence of lung cancer in never-smokers by utilizing data from six large cohorts primarily from the United States and Sweden from 1971 to 2002. Age-adjusted incidence rates by sex for people aged 40–79, ranged from 4.8 cases for men in the Swedish cohort to 20.8 per 100,000 person years for women in the California Teachers Study cohort; however, the study was not designed to answer whether the incidence rates were increasing over time [22]. The incidence rates were higher for women than they were for men, but this does not answer whether women who never smoke are at an increased risk to develop lung cancer compared to men [23]. Thun et al. tried to answer this question of whether the incidence rate of lung cancer was increasing by comparing historical

data to more recent analyses. Taking data from 13 large cohorts and 22 cancer registries they examined cohorts with low prevalence of smoking either reported from 1983–1987 or historical cases of US women in the 1935–1940 Connecticut Tumor Registry. It was noted in women of European descent the age-standardized rate for lung cancer in never-smokers was 9.7 per 100,000 women, which was similar to Basque women at 8.6 in the 1980s and 8.7 in US women in the 1930s [18]. Although this study demonstrated no increase in the incidence of lung cancer in never-smoker women over time, it had limited numbers to report incidence rates accurately for Asians, and African Americans, and made no comment on men. A single center study in Asia reported a significantly increased incidence of lung cancer in never-smokers spanning three decades from 1970 to 2000 that went from 15.9 % to 32.8 % over this time period [24]. Caution should be taken; however, as this study reported only proportions, not incidence rates or standardized rates. Unfortunately, to date lung cancer incidence in never-smokers has yet to be studied in an accurate and comprehensive manner given the lack of smoking data in the majority of cancer registries.

Several large studies have examined death rates from lung cancer in never-smokers stratified by sex and ethnicity, specifically examining temporal trends as well as risk. Death rates by sex were examined in the two large American Cancer Society (ACS) studies, Cancer Prevention Study (CPS) I (1959–1972) and II (1982–2000), to give age-specific and age-standardized death rates for 460,000 never-smokers, aged 35–84, all within the US, Puerto Rico, and Guam. They found age-standardized death rates were significantly higher in men at all ages in the first CPS cohort. In the second cohort the higher death rate in men was only seen in those age 60 and above, which may have been related to the decreasing death rate among men, ages 35–69, and the increased death rate in women, ages 70–84 [20]. The study mentioned previously by Thun et al. included CPS I and extended the coverage of CPS II by 4 years and reported higher death rates in men aged 40 and over in those of European and Asian descent. The number of deaths in African American men was small, making it difficult to reliably comment on all age groups. In never-smokers of European descent in the US, the calculated risk to develop lung cancer was estimated at 1.1 % for a man and 0.8 % for a woman before the age of 85 [18].

Limited data exists on comparative analysis between ethnic groups among never-smokers with lung cancer. In the ACS cohort analysis, incidence was only significantly higher for African American women aged 40–69 compared to men and women of European descent [18]. Gomez et al., in a population-based case-control study from Northern California, found that from the years 1998–2003 and 2005–2008, a higher proportion of female never smokers with lung cancer were Asian Pacific Islanders (API) and Latinas compared to non-Hispanic whites. Although this was a small study, hazard ratios were calculated and a cox proportional hazard model demonstrated that mortality rates in U.S. born Latinas and female API were 2.1 and 1.7 times higher, respectively, than non-Hispanic whites [25]. Caution in interpretation must be taken given significant variance between regions. This was illustrated by Liu et al. who found significant variation in the incidence of lung cancer in never-smokers in China, even in neighboring cities. Taking all the cities together the death rate was 0.5 per 1000 never-smokers compared to 1.5 in smokers [17].

## Potential Risk Factors in the Development of Lung Cancer in Never Smokers

### *Second Hand Smoke*

The IARC as well as several authors list second hand smoke (SHS) as carcinogenic with an excess of lung cancer from SHS as high as 25 % [26–28] (Table 1). A descriptive study found that amongst those with SHS exposure approximately 22 % were men and 88 % were women [29]. While frequency data does not evaluate association or risk there have been several case-control studies that have calculated

**Table 1** Selected risk factors in the development of lung cancer in never smokers

| Risk factor | Risk ratio | Comments | References |
|---|---|---|---|
| Second hand smoke | 1.34 | Prospective nested case control in Europe | [27] |
| | 1.23 (spouse)<br>1.27 (workplace) | Pooled analysis from two case controls US & Europe | [31] |
| | 2.1 | Case control from Toronto | [32] |
| | 1.34 | Prospective cohort study in Japan | [34] |
| Residential radon | 0.18 per 100 Bq/m3 | This is an estimated odds ratio based on unit of radioactivity exposure from radon measured in Becquerel (Bq) | [43] |
| Indoor air pollution (biofuel) | 2.15 | Meta-analysis of 25 case control studies of household coal | [54] |
| Occupational exposures | 3.49 asbestos<br>2.48 paint dust | Prospective cohort study in the Netherlands | [58] |
| Lung disease | 2.93 | Asthma | [57] |
| Genetic susceptibility | 1.95 | Family history of lung cancer in first degree relative | [65] |
| | 1.62-Heterozygote<br>2.35-Homozygote | 5p15.33 Asian females | [73] |
| | 5p15.33:<br>White-1.15<br>Asian-1.23 | Pooled analysis of 21 case control studies of Whites and Asians. 15q25.1 & 6p21.33 were not significantly associated with risk of lung cancer in never smokers. | [77] |
| | 0.68 | 18p11.22 447 Korean never smokers | [79] |
| | 1.46 | 13q31.3 multicenter study in US | [78] |
| | 1.32<br>0.85<br>1.16<br>1.19<br>0.86 | 10q25.2<br>6q22.2<br>6p21.32<br>3q28<br>17q24.3<br>Study population were Asian women | [80] |
| | 0.45 | MSH2 | [89] |

*MSH2* mutS homolog 2

odds ratios and utilized unconditional regression analysis to help answer this question. Unfortunately, not every study lists this information in the analysis; therefore, caution should be taken for over estimation of odds ratios [30]. In these case-control studies SHS for the most part has been subdivided into home, workplace, or social with differences noted in odds ratios from one setting to the other, but all with odds ratios greater than 1 and higher risk noted with combined exposures noted in regression analysis [31–34]. As SHS is often assessed by interview from smoking partner, non-smoking partner, or next-of-kin the validity of these measures as well as non-smoker status have been brought into question; however, misclassification is likely low [35, 36]. Other studies have been able to demonstrate dose response by SHS intensity and duration [31, 34]. One author also noted an increased risk if exposed to SHS prior to the age of 25 [37].

## *Indoor Pollution*

Indoor air pollution includes: radon from soil and water, products of combustion such as coal, chemicals from household products, and biological agents such as mold among many other sources [38]. This is a fairly large category of which the focus in this section will be on those that are known to cause an increased risk of lung cancer.

Radon is a decay product from radium that is found in rock and soil. Radon can further decay into polonium that enters the air and water and emits alpha particles, which can cause DNA damage [39]. While it has already been established that in miners radon exposure can lead to lung cancer [40], less well defined is whether low-indoor radon levels are associated with increased risk as well. The following presentation of studies will examine different methods of measuring association and risk with varying results to answer this important question.

Krewski et al. in a combined analysis of seven large case-control studies in North America, including 4081 cases and 5281 controls, demonstrated with estimated odds ratios (EOR) that residential exposure to radon in general was associated with the lung cancer risk. It should be noted that although the odds ratios were numerically positive and statistically significant in two out of the seven studies, in the pooled analysis there was no statistically significant difference [40]. Arguably, relative risk is a better measure to assess causation than excess risk of disease as had been used in the study above [41]; however, both assess association and to assess causality is more complex requiring the achievement of specific criteria [3]. Sandler et al. was not able to find statistically significant excess relative risk of lung cancer related to radon exposure at any level [42]. This study, however, had significantly lower radon levels on average that did not even meet the actionable level suggested by the EPA. This study was also underpowered to assess whether there was any synergistic effect in smokers. In contrast, two separate studies from Darby et al. and Leuruad et al. found the relative risk of lung cancer in never smokers increased with radon exposure [43, 44]. One study identified a potentially high-risk group as those

who were homozygous for glutathione-S-transferase M1, an enzyme responsible in neutralizing reactive oxygen species [45].

Several studies have established a large variation in the incidence of lung cancer in Asian countries that has been postulated to be possibly due to unreported tobacco use, but also likely due to indoor air pollution [17, 18]. Indoor air pollution has been examined as a global health issue associated with an increased risk of lung cancer along with other respiratory illnesses [46]. The risk for lung cancer varies, but has been found largely in developing countries [6, 7]. Coal and wood smoke are now recognized by the IARC as a human carcinogen [47]. The use of indoor combustion products is highest in Africa and South East Asia at greater than 60 % compared to the Americas and Europe at less than 20 % [48]. Kleinerman et al. interviewed men and women from two prefectural areas in Northwest China in a case-control study on the use of coal and biomass fuel in heating and cooking in controls and lung cancer patients. They adjusted for smoking status and frequency matched for age and sex, and find a modest increased risk for those with the highest exposures [49]. In a retrospective analysis from the Yunnan Province of China, the authors found a significantly increased absolute and relative risk of dying from lung cancer in those who utilized smoky coal versus smokeless coal [50]. Coal use was also evaluated in a large case-control study in participants from Eastern/Central Europe and the United Kingdom where there was an increased risk observed when solid biofuels (coal or wood) were used for cooking [38]. This was confirmed in a large meta-analysis performed of 25 case control studies that covered cases from Africa, North America, Europe, India, Mainland China and Taiwan. Although there were differences in the risk of lung cancer by regions, the overall trend was an increase in lung cancer risk in particular in parts of China and Taiwan [51]. A transition to ventilated stoves was associated with a decreased in lung cancer incidence in at least one analysis from China [52].

## *Occupational Exposures*

Several authors have examined occupational exposures such as pesticides, grain elevator dust, wood dust, smoke soot or exhaust as risk factors for lung cancer in never-smokers [32, 53, 54]. A large prospective cohort study of men from The Netherlands assessed cumulative probability of exposure to four specific known carcinogens at the work place reported by the IARC: asbestos, paint dust, polycyclic aromatic hydrocarbon (PAH), and welding fumes [54]. After adjusted for age and smoking status in the final analysis they found a significantly increased risk if exposed to asbestos or paint dust, with asbestos having the highest risk. They also found that the tested population was fairly representative of the Dutch population and that 11.6 % and 1.7 % of the lung cancers were attributable to asbestos and paint dust, respectively [54]. None-the-less, occupational exposure does not explain fully lung cancer in never-smoker as it has been shown that individuals without any occupational or environmental exposure can develop lung cancer [12, 29].

## *Lung Disease*

Epidemiologists have studied whether specific lung conditions or infections are associated with an increased risk of lung cancer, but with conflicting data likely due to the confounding factor of smoking status. One study found no increased risk for lung cancer in never-smokers who had emphysema, chronic bronchitis, asthma, pneumonia, or tuberculosis [32]. Another study found asthma in never-smokers was associated with increased risk of lung cancer with an odds ratio of 2.93 compared to those without asthma [53]. An increased risk has also been seen in those with a history of tuberculosis infection with an odds ratio as high as 3.5 in never-smokers, particularly for disease on the same side of the previous infection [55, 56]. The association in individuals with pulmonary fibrosis is also unclear [57–60].

## *Radiation Exposure*

In patients exposed to ionizing radiation either as treatment for breast cancer or Hodgkin's disease there is an increase risk in the development of lung cancer [61–63]. A recent study reports that molecular rearrangement of the *RET* gene may explain a small percentage of radiation induced adenocarcinomas of the lung in never-smokers [64].

## *Genetic Factors*

Environmental exposures as described above appear to increase the risk of lung cancer in never-smokers and genetic factors play as role as well. Nitadori et al. performed a large prospective cohort study of a Japanese population to examine whether family history in a first degree relative increased the risk of lung cancer. A family history of lung cancer was associated with a significant increase in risk of lung cancer in both ever and never smoker groups, although the risk was higher in women and in never-smokers [65]. It should be noted this study controlled for SHS, but did not compare hazard ratios between ever-smokers versus never-smokers to examine whether there was a significant difference between groups. Several other studies have also reported similar results in cohort or case-control analyses [32, 33, 53, 66, 67].

On the molecular level, Bell et al. noted a family of European descent with a germline *epidermal growth factor receptor* (*EGFR*) mutation. The proband as well as his brothers, had a T790M *EGFR* germline mutation, but the two brothers did not have lung cancer. The proband at surgery was noted to have five separate tumors that were analyzed for somatic mutations in the *EGFR* domain with the missense L858R mutation and in-frame deletion delL747-T751 noted [68]. Ohtsuka et al.

identified a separate germ-line mutation in *EGFR*, V843I, which was found in multiple generations as an identical mutation. As in the previous study, in addition to the germline mutation, somatic mutations were identified including L858R. Interestingly, the V8438I mutation confers resistance to tyrosine kinase inhibitors as has been described for the T790M mutation; however, the exact mechanism for this resistance or increased susceptibility to lung cancer from either mutation has yet to be elucidated [69]. Recently, a unique *HER2* germline mutation, G660D, was identified in a Japanese family with lung cancer in multiple generations [70].

While these last two studies have examined the potential heritability of lung cancer risk at a specific gene level, other studies have used more traditional linkage analysis strategies to identify loci of interest that might confer risk to the disease [71]. One study utilized comparative genomic hybridization analysis to determine that in never-smokers of Chinese descent with lung cancer, gain of 16p was frequent, though loss of 16p was identified in an earlier study that was not restricted to patients of Chinese ancestry [71, 72]. Several scientists have performed genome wide association studies (GWAS) in never-smokers utilizing single nucleotide polymorphism array data and have identified 5p15.33 locus (*TERT-CLPTM1L*) as one that confers an increased risk of lung cancer [73–75]. There have been several other loci identified; however, they have not been consistently replicated, perhaps due to ethnic or environmental exposure differences [76, 77]. This was seen in two separate studies where 13q31.3 (*GPC5*) was identified in an American population [78] and 18p11.22 (*FAM38B*) in a Korean population [79]. A large GWAS among Asian females found several novel chromosomal aberrations at 10q25.2 (*VTI1A*), 6q22.2 (*ROS1 & DCBLD1*), and 6p21.32 (*HLA-DRA*) when compared to controls [80]. They also confirmed two other mutations, 3q28 (*TP63*) and 17q24.3 (*BPTF*), reported in three separate studies [81–83]. Other scientists have focused on specific genes that have largely been associated with the metabolism of tobacco related carcinogens in the cytochrome P450 system. The data has been inconsistent with some [84, 85] reporting an increased risk in those with CYP1A mutations while others have refuted this finding [86]. Other studies have looked at DNA repair with some data to support an increased risk in those with the lowest DNA repair capacity [87], while others have implicated polymorphisms in the ataxia telangiectasia mutated gene [88] or mismatch repair gene MSH2, in particular if associated with SHS exposure [89, 90]. Govindan et al. performed whole genome sequencing as well as whole transcriptome sequencing, on multiple lung cancer surgical specimens, including in some tumors from never smoking patients. This study was able to demonstrate significant difference in mutation rate between smokers and never smokers indicating a different oncogenic process [91].

## Pathology

The topic of histological subtype has been well studied with the majority of data reporting adenocarcinoma as the most common histological type in never smokers [6, 7, 22, 92, 93]. In a review paper on lung cancer in never-smokers

Samet et al. presents relevant theories of why a trend for an increase in adenocarcinoma has been observed, even in smokers, and especially in women, including change in puff volume that may distribute carcinogens differently within lung tissue as well as increased nitrate levels due to greater combustion of tobacco material within the cigarette, which he asserts also impacts never-smokers through side stream smoke [12]. One study looked at subtypes of adenocarcinoma as they correlate with common mutational status among never-smokers [94].

## Driver Mutations

Considerable research has led to identification of "driver mutations" in adenocarcinoma of the lung and two, *EGFR* and *ALK*, already have FDA approved therapeutics. Others such as *ROS1*, *BRAF* and *HER2* are targetable with drugs on the market for other indications and more, including *KRAS* and *RET*, with agents that are in ongoing investigations. Specifics on molecular profiling and receptor cell signaling will be discussed in detail in chapters later in this book.

Estimates of actionable mutational frequency in never-smokers vary by ethnicity or region (Fig. 1) with reports as high as 90 % in a single-center institution of Chinese women with lung cancer that included analysis for *EGFR*, *ALK*, *HER2*, and *KRAS* [94] to 29.4 % EGFR mutant in a recent evaluation of 907 patients with lung cancer from India [95]. In general, mutations within *EGFR* are identified in approx-

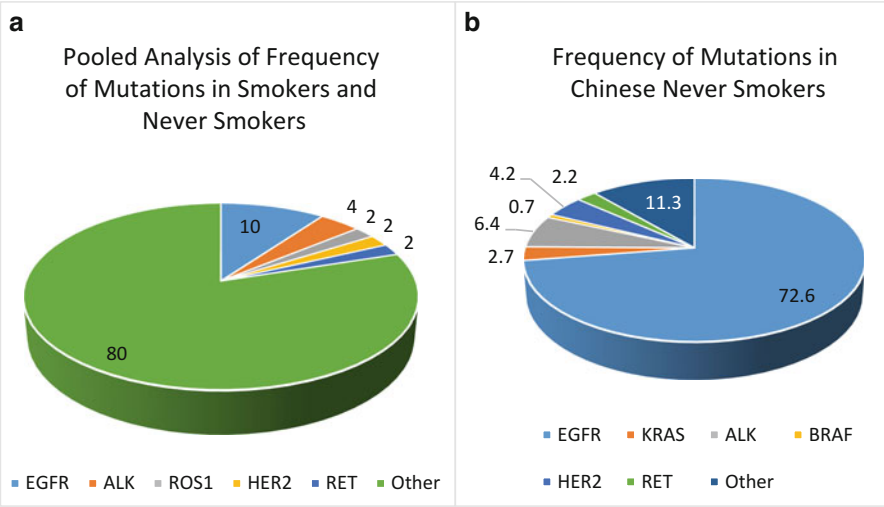


**Fig. 1 Mutations are more common in never smokers with adenocarcinoma.** In figure (**a**), percentages are displayed of the frequency of mutations in adenocarcinoma that includes smokers with never smokers. Figure (**b**), although inherent biases exist in single center studies, this single center study in China illustrates the proportion of identifiable mutations in a population of 408 never smokers with adenocarcinoma

imately 10 % of lung adenocarcinomas, but at a much higher frequency in never-smokers [96]. Another example is that HER2 exon 20 insertion mutations constitute approximately 2 % of NSCLC adenocarcinoma mutations but are more common in women, with adenocarcinoma who were never-smokers [97, 98].

Other significant mutations found in lung cancer, with a higher frequency in those who develop lung cancer as never-smokers, are ALK and ROS1 [99–101]. ALK mutations represent approximately 4 % of lung adenocarcinomas while ROS1 is around 2 %. Patients with this mutation also appear to be younger, never smokers, and have adenocarcinoma [97]. RET alterations are found in roughly 2 % of adenocarcinomas of the lung with individuals typically younger and never-smokers [64, 102, 103].

## Prognosis

Survival data for lung cancer patients who are never-smokers as compared to smokers is conflicting. Subramananian et al. in a single-center case-control study did not find a survival difference between smokers and never smokers [104]. Nordquist et al. in a single center study however, reported 16 % vs 23 % 5-year survival rates in smokers compared to never-smokers. Smoking was a negative predictive value on regression analysis in another study [105]. A very large retrospective study by Kawaguchi et al. utilizing 15,185 Japanese individuals from one national registry and 13,332 Caucasians from a cancer registry in Southern California found a statistically significant survival advantage for Japanese never-smokers and a trend for Caucasian never-smokers compared to smokers with lung cancer [106].

## Summary

Lung cancer in never smokers as a separate entity is the seventh leading cause of cancer related mortality. There appears to be racial variation in the incidence and mortality that require further research. Established risk factors include second hand smoke, several environmental toxins and potential genetic predispositions, but much work still needs to be done in this area. Whatever the inciting event, it appears adenocarcinoma is the most common histological type and can be associated with a variety of somatic mutations with important therapeutic implications.

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