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A COMPREHENSIVE REVIEW OF THE PREVALENCE, DETERMINANTS, AND CHALLENGES OF SMALL-CELL LUNG CANCER IN NEVER-SMOKERS

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Abstract

Small-cell lung cancer is an aggressive neuroendocrine malignancy strongly linked to smoking; however it's occurrence in never smokers could indicate the influence of some environmental, occupational, genetic/molecular factors which aren't often considered. This review aims to not only gain a broader picture on small-cell lung cancer but also investigate possible risk factors as well as relevant diagnostic and public health strategies. A comprehensive literature search was conducted using Web of Science, EMBASE and Google Scholar. Primary articles of focus included studies on lung cancer in never-smokers, small-cell lung cancer, risk factors associated with lung cancer in never smokers. Relevant studies were overviewed to identify important information. Study findings indicate several possible risk factors among never-smokers such as occupational exposures (e.g. asbestos, polycyclic aromatic hydrocarbons, wood dust etc.), air pollution, second-hand smoke as well as genetic and molecular influences. Findings also suggest possible predilection for older age and female demographic, patients with history of autoimmune diseases and regional variations. According to the findings it is also suggested that the prevalence of never-smoking small-cell lung cancer cases has been on the rise over the past few decades. Understanding the risk factors for small-cell lung cancer among the never-smoking population is critical for refining lung-cancer preventive strategies, diagnostic tools and public health measures.

INTRODUCTION

Lung cancer in recent years has remained the second most commonly diagnosed cancer with up to 2.2 million new cases in a year and also remains the leading cause of cancer death with up to 1.8 million deaths in 2020 [1]. Small cell carcinoma accounts for about 14% of the cases of lung cancer, among which 95% are found to be associated with smoking, with this in mind there is still room for consideration when it comes to the remaining 5% of non-smoking related potential cases. Among such cases it is estimated that approximately 2-3% of small cell lung cancer occurs in patients who are never-smokers [2-4]. To better understand this minority it is important to delve into potential environmental, occupational, genetic and molecular factors which may influence the development of these cases. For instance research has demonstrated that individuals from lower socio-economic classes have greater odds of developing lung cancer, including small-cell lung cancer; such findings could suggest that besides smoking other factors such as lack of adequate healthcare, higher environmental and possibly occupational exposures and chronic stress may also influence the chances of developing lung cancer [5]. Similarly factors such as race and genetics have also found to have relation with the variation in incidence of different histological types of lung cancers [6]. To support this plausibility; study in the past has shown difference in incidence and death rates by lung cancers between black and white men with black men having a higher general incidence and death rate but interestingly a lower incidence than white men when it comes to small-cell lung cancer in particular [7]. A study compiling 1040 cases of small-cell lung cancer found that only 23 patients (2% of total patient population) were never smokers, and 83% of those patients were presumed to have developed the condition de-novo while 17% of the patients had acquired the condition via transformation as a result to resistance to erlotinib treatment of EFGR-mutant lung carcinomas [8]. The uncertain nature of majority of these cases in which small cell lung cancer arises without any history of smoking is one which is worth delving into in a scientific perspective to better understand the possible mechanism and causes of its occurrence.

Currently it is estimated that 25% of lung cancers are among patients who are never smokers, this is important to consider because with the development of smoking prevention programs we can expect the incidence of such cases to increase [9]. For the development of these cases various risk factors including second hand smoke, genetics, hormones, somatic mutations such as EFGR, HER2, ALK rearrangements, abnormalities in DNA repair and inflammatory response genes have been described, although adenocarcinoma of the lung has been found to be the predominant condition to arise from these risk factors, it is still worth noting the minority of affected patients that go on to develop small-cell lung cancer [9]. Many sources in recent times have shown the prevalence of smoking to be decreasing in many areas of the world [10-12], it has also been shown that risk factors such as occupational exposures have been on the rise [13-15] which is why looking into the situation with a futuristic prospective, it is ideal to consider risk factors unrelated to smoking which may gain more relevance moving forward when it comes to the development of small-cell lung cancer and other cancers in general with the aim of developing possible primary preventive tactics. Recent study in Korea also found that history of never-smoking among small cell lung cancer patients may actually be associated with a worse overall survival rate [16]. The combination of possibly increasing incidence, increased severity, and mechanistic uncertainty warrants further investigation into the matter.

EPIDEMIOLOGY

Cases of small cell lung cancer in never smokers

Studies have been conducted in the past that detail cases of small-cell lung cancer in non-smokers, for instance a study of 2 cases found one case comprising a middle-aged patient with minimal smoking history but significant second hand smoking exposure over a 2 year period, the other case consisted of an older women with past history of treatment for stage 2 breast cancer 24 years before diagnoses and primary biliary cirrhosis 11 years before the diagnosis of small-cell lung cancer, immunohistochemical stains for the first case were positive for chromogranin, synaptophysin, thyroid transcription factor-1 (TTF-1), and cell adhesion molecule 5.2 (CAM 5.2) and were negative for CK7, CK20, cytokeratins, and CD99 on biopsy of right supraclavicular mass and positive for cytokeratin AE1 and AE3 and diffusely positive staining for synaptophysin and TTF-1, on biopsy of the left supraclavicular lymph node 15 months later, meanwhile the second case was found to be positive for CK7, MOC31, neuron specific enolase (NSE), synaptophysin, and CD56 and were negative for CK20, TTF-1, chromogranin CD57, and p53 on immunohistochemical testing [17], these 2 atypical presentations of small-cell lung cancer suggest possible associations with risk factors like second hand smoking, past history of cancer, auto-immune diseases and variations in tumor biology. The possible association of auto-immune diseases with the development of small-cell lung cancer in non-smokers may be further supported by a study which found the development of small-cell lung cancer in a case where the patient had developed interstitial pneumonitis as a result of underlying systemic sclerosis [18]. A case series consisting of 19 cases of small-cell lung cancer in non-smokers had 18 female patient and a single male patient which may suggest possible sex predilection, besides this the median age was of 75 which could also point towards cases of small-cell lung cancer in non-smokers being more predominant in the older age groups, the residential radon exposure, among the patients (195 $Bq.m^{-3}$) was also higher than the action levels recommended by World Health Organization (WHO) [19], which is another major risk factor for the development of lung cancer. As mentioned previously the fraction of patients suffering from small-cell lung cancer who are never smokers is about as low as 2-3% in most cases, surprisingly however a study conducted in china among 303 patients of small-cell lung cancer found 69 (22.8%) of the patients to be never-smokers which is a significantly greater proportion than what is normally presented, which could suggest possible increasing prevalence in China in particular, also contrary to previously mentioned study, the overall survival of these patients was found to be better than those who had smoking history [20]. Another study comprising 32 cases of small-cell lung cancer in never smokers also had a median age of 75 further supporting the possible older age predilection for its development, uniquely, it also found that indoor radon which is generally considered to be the biggest risk factor for lung cancer development in never-smokers, may not be associated with small-cell lung cancer characteristics at diagnosis [21-23]. From these cases although small-cell lung cancer in never-smokers remains rare, it is clear to see that there may be some signs of increasing prevalence, and associations with some consistent risk factors such as second-hand smoking, radon exposure, environmental influences, tissue biology, autoimmune disease history etc.

Brief comparison between smokers and never-smokers with lung cancer

Before delving further into risk factors for small-cell lung cancer in non-smokers it is important to consider basic differences between smoking and never-smoking lung cancer patients in general that have been previously observed including differences in genetic expression, genetic mutations, polymorphisms, ethnic and sexual differences [24].

Variations in genetic expression have been found between smokers and never-smokers with lung cancer. For example, a greater expression of EGFR, Ki-67 and HTERT in smokers while never-smokers mostly expressed p-AKT and p27. It is worthy to consider the lower sample of patients in these studies [25]. Moreover, a study using RNA microarrays showed that smokers with lung cancer often have pre-existing changes in the gene expression of their non-cancerous lung tissues, such changes are absent among never-smokers. This suggests that smoking "sets the stage" for lung cancer among smokers whereas when it comes to non-smokers, lung cancer can occur in non-cancerous tissue, without any prior history of smoking, these pre-existing changes in gene expression may also explain why lung cancer is more easily diagnosed in smokers [26].

Key differences in genetic expression, mutations and genetic polymorphisms between lung cancer in smokers and never-smokers suggest that they are two distinct diseases. Smokers tend to have more chromosomal aberrations, while never-smokers show more cytosine hypermethylation, genetic polymorphisms, such as in CYP1A1 and CYP1B1 genes, influence cancer risk differently in each group. Never-smokers appear to be more responsive to targeted therapy with up to 50% potentially treatable cases compared to 10% in the case of smokers. These aforementioned differences may suggest that lung cancers in these two groups are genetically distinct [27, 28].

Ethnic differences in lung cancer occurrence between smokers and never-smokers have also been observed. For instance, on comparison of lung adenocarcinoma occurrence between patients of East Asian and European ancestry, it was found that lung cancer in never-smokers was much more common in the Asian population (30-40% of cases) as compared to the Caucasian population (10-20% of cases). EFGR mutations were more common in East Asian patients while European patients had more mutations in driver genes like KRAS. Overall, the tumor mutation burden was lower for both populations in never-smokers as compared to smokers [29, 30].

Previously mentioned reported cases of small-cell lung cancer in never-smokers had a common theme of female predominance among the patients, as is consistent with other case series as well [31], this is despite the fact that recent trends have demonstrated that the overall proportion of small-cell lung cancer cases (including smokers) have been increasing more noticeably in men rather than women [32]. This further suggests possible female predilection for small-cell lung cancer development among never-smokers compared to smokers.

Epidemiological differences between smokers and non-smokers continue to be demonstrated, such as less incidence of lung cancer among non-smokers at younger age, greater incidence of lung cancer among never-smoking women, higher incidence of never-smoking lung cancer among Asian and African American, and even geographical variations such as greater incidence in countries near the Pacific Rim and China [33].

Frequency and differences in never-smoking small-cell lung cancer patients across literature

Studies in the past have documented both non-smoking and smoking related causes of lung cancers including small-cell lung cancer among patients of varying socio-economic backgrounds and exposed to different kinds of risk factors. A 1987 study on different histological subtypes of lung cancer among Chinese women in Hong Kong found that among 202 patients with never-smoking lung cancer, 9 of them had small-cell carcinoma. Radon, air pollution, family history of lung cancer and asbestos were the major risk factors among non-smokers [34]. Another study from 1988 on incidence of different histological subtypes of lung cancer consisting of a total of 919 cases of lung cancer with 59 (6.4%) cases occurring in non-smokers, out which 23 (2.5%) were male with 6 cases being of small-cell lung cancer and 31 (3.3%) were female with only 1 case being of small-cell lung cancer, this gender wise distribution is interestingly different from that found and described in more recent study [35]. A 2002 population based study comprising of a total of 20,561 cases with 738 (3.5%) never-smokers found 229 (1.1%) never-smokers with lung cancer were males while 205 (1%) were female, 36 of those patients were cases of small-cell carcinoma in males while 45 of them were cases of small-cell carcinoma in females, which is more consistent with the gender wise distribution found in recent studies [36], although the proportion of never-smoking patients with small-cell lung cancer is less than recently reported, which could possibly indicate an increase in incidence of small-cell carcinoma in never-smokers overtime. A 2005 study conducted in Korea reported 1357 lung cancer cases with 110 (8.1%) of patients being never-smokers among which only 4 cases were of small cell lung cancer [37].

In more recent times; a 2022 study consisting of microscopically confirmed and diagnosed cases of lung cancer in the state of Florida (USA) between the years 2014-2018 found that out of the 9,823 patients which were never-smokers diagnosed with lung cancer, 603 (6.1%) of them were diagnosed with small-cell lung cancer which is a much greater portion of never smokers having the diagnoses as compared to the previously mentioned studies form decades prior, which could possibly suggest a rise in prevalence in more recent times [38]. Similar to patients with smoking history, the dominant race among never smokers with lung cancer was white/Caucasian, however that could be partially attributed to the sample population and area of study, the age group with the highest prevalence of lung cancer in never smokers was 75+ whereas it was a slightly younger age group of 65-74 for smokers, females were found to be more affected by lung cancer among the non-smoking population whereas males were slightly more affected among the smokers, which further supports previous evidence of slight female predominance in lung cancer among never-smokers [38]. A study from 2021 which comprised of microscopically diagnosed cases of lung cancer from 2011-2016 among 7 different states in the USA, found that among 129,309 cases of lung cancer, 12.5% of them were never smokers which is also a greater prevalence than that found in older studies, also among men and women who were diagnosed with small or squamous cell cancer, 6-8% of them were never smokers, once again a higher proportion of never-smokers with lung cancer was found among female population [39]. Recent literature has also at times shown a lower prevalence of never-smoking patients among cases of small-cell lung cancer as compared to other studies, for instance a multi-center cohort study reported only 1.8% of small cell lung cancer patients as never-smokers, and never-smokers had a lower mutational burden with lower rates of TP53 mutations [40]. Although over all there seems to be a rise in number of cases of small-cell lung cancer in never-smoker when compared with studies from decades ago, in more recent times the trend may be more stagnant, a cohort study reported that although there was a significant increase in never-smoking lung cancer cases between 2011 to 2018, and also an increase in newly diagnosed cases of small-cell lung cancer, the overall trend for never-smoking small-cell lung cancer patients had not changed much from 15.5% of small cell carcinoma cases in 2011 to 16.8% in 2018 [41]. While these numbers are stagnant it is still worth noting the much higher prevalence found in the study when compared with previously mentioned literature which supports not just variation in the number of cases but also a possibility of an increase in cases over time when looking at the wide spectrum of available literature. It is also important to consider the prognosis of these patients, in which case it was found that never-smokers with lung cancer overall had worse outcomes compared to smokers. [41].

Broadly speaking, while older studies have documented a lower prevalence of small-cell lung cancer among never-smokers, recent literature suggests an increase in cases which are more predominant among women, although there is possibility of some stagnancy in the growth of cases as we move closer to the present, that being said there isn't enough literature to be conclusive on such a statement either [34-41]. Risk factors such as radon, second-hand smoke, air pollution, family history, and asbestos have been consistently associated with never smoking lung cancer although a deeper dive into potential risk factors would still derive benefit in understanding the overall prevalence of never-smoking small-cell lung cancer today [34, 41]. Despite regional and demographic differences, never-smokers often experience worse outcomes than smokers with lung cancer which further highlights the need for expanded research on risk factors and prognosis [33-41].

PATHOPHYSIOLOGY

Environmental factors contributing to small-cell lung carcinoma in never-smokers

1. Air pollution

In the past it has been observed that never smokers with lung cancer have an increased association with air pollution exposure as compared to smokers having lung cancer [42]. A meta-analysis conducted among 18 studies which aimed to examine the relationship of $PM_{2.5}$ and PM_{10} (Particulate matter) with lung cancer incidence and mortality found that the lung cancer risk associated with $PM_{2.5}$ was the lowest with current smokers, followed by never smokers, followed by former smokers [43], Another meta-analysis compiling 21 cohort studies found that long term exposure to $PM_{2.5}$, NO_2 (nitrogen dioxide), NO_X (nitrogen oxides), and SO_2 (sulfur dioxide) may be associated with an increased risk of lung cancer, these positive relations remained even when restricted to never-smokers, additionally the association of fine particulate with lung cancer was found to be stronger in never-smokers [44]. These studies further emphasize and strengthen the possible relationship between air pollution/particulate exposures with lung cancer in never-smokers. It is important to acknowledge however that an increased incidence association in regards to lung cancer and air pollution in never-smokers doesn't necessary equate to an increased association with mortality as a meta-study showed that although never-smokers with lung cancer had an increased incidence of $PM_{2.5}$ exposure, mortality associated with $PM_{2.5}$ exposure still remained highest in smoking lung cancer patients [45].

2. Radon

Studies have suggested that residential radon exposure may be more harmful than environmental tobacco smoke in the development of lung cancer among never smokers; this includes but is not specific to small-cell lung cancer [46]. There is some discrepancy however between different literatures; a meta-study suggests that while in some studies there is an association between lung cancer development in never smokers and radon exposure, there are other studies that also suggest otherwise [47]. A collaborative analysis found that the increase in risk per 100 Bq/m^3 of measured radon for small-cell lung cancer was higher (31.2%) than all other histological subtypes combined (2.6%), which suggests that there might be a higher risk of small-cell lung cancer with increased radon exposure as compared to the other histological subtypes [48]. A pooling study observed the highest median radon concentration by histological type was observed for "other uncommon histological types" (207 Bq/m3) followed by small-cell lung cancer (187 Bq/m3) [49]. There is also evidence which suggests an increased exposure to residential radon can lead to the expression of pathogenic EGFR variants and ALK translocations along with an increased risk of small-cell lung cancer among never-smokers [50-53]. A meta-analysis of case control studies showed that residential radon exposure was notably linked to an increased risk of small-cell lung cancer in never-smokers, with an odds ratio of 2.03 (95% CI, 1.52-2.71), the highest among all lung cancer histological types. As radon levels surpass 100 Bq/m³, the risk of small-cell lung cancer rises by 19%, emphasizing the heightened danger even at relatively moderate exposure levels [54]. These findings highlight the significant role radon can play in the development of small-cell lung cancer, particularly in individuals who have never smoked.

3. Second-hand smoke

There are some cases of lung cancer among non-smokers which suggest second-hand smoking to be the only exposure/risk factor found in the case reports [55]. Needless to say, second-hand smoking has been well implicated as a risk factor for lung cancer [56]. A study investigating tobacco smoke exposure among non-smoking lung cancer patients suggests 15-35% of non-smoker cancers could be related to second-hand smoke [57]. It has also been suggested that family members of smokers could be at an increased risk of lung cancer, for instance women married to smokers could have up to a 27% increased risk of lung cancer [58]. Likewise, there is a fair amount of literature which displays the relation between second-hand smoking and lung cancer in never smokers [59, 60]. However, there is possibly a need to specifically investigate this relationship in the context of small-cell lung cancer in particular, as literature still seems to be limited in that aspect.

Occupational factors contributing to small-cell carcinoma in never-smokers

1. Asbestos

Asbestos is a hazardous occupational exposure for never-smokers with lung cancer, and its potential impact on mortality further emphasizes its severity. This is supported by findings showing that asbestos exposure alone increased lung cancer mortality among non-smokers (RR = 3.6; 95% CI, 1.7–7.6), highlighting the significant risk it poses in this population [61]. A review of seven case-control studies, including 3,231 small-cell lung cancer cases, provides evidence of the association between occupational asbestos exposure and small-cell lung cancer risk. Four of these studies reported smoking-adjusted risks, and a pooled analysis of six studies focusing on men found a significantly increased risk of small-cell lung cancer (pooled OR = 1.89; 95% CI, 1.25–2.86) with moderate heterogeneity (I^2 = 46.0%). These findings suggest that occupational asbestos exposure plays a significant role in increasing the risk of small-cell lung cancer in men [62, 63]. These findings emphasize the need for further research into the impact of occupational asbestos exposure on small-cell lung cancer, especially in never-smokers.

2. Other workplace and occupational exposures

Occupational exposures continue to show significance in lung cancer risk, for instance; occupational exposure to welding fumes has shown increased incidence and mortality-based risks for tracheal, bronchial and lung cancer [64]. Cohort study supports occupational carcinogens effects on the development of lung cancer [65]. Exposure to occupational toxins like asbestos, chromium, and arsenic has been linked to an increased risk of lung cancer, though the association is weaker among never-smokers [66, 67]. A study conducted in Holland found that individuals exposed to asbestos had a 3.5 times higher risk of developing lung cancer, even after adjusting for factors such as age, smoking, and vitamin intake [68]. According to a pooled analysis of 14 case control studies, diesel engine exhaust exposure which is a common occupational exposure among truck drivers, forklift workers, railroad workers etc. has also been found to have a strong association with lung cancers including small-cell lung cancer [69]. In another pooled study, several pair wise joint effects were observed for small-cell lung cancer in women. Notably, exposure to polycyclic aromatic hydrocarbons (PAHs) and silica was linked to an increased risk (OR = 5.12; CI: 1.77–8.48), as was exposure to asbestos and silica (OR = 4.32; CI: 1.35–7.29). Additionally, the combined exposure to PAHs and silica showed a synergistic effect (RERI = 3.45; CI: 0.10–6.8), indicating that their joint impact on lung cancer risk was greater than the sum of their individual effects [70]. A meta-analysis of eleven studies, including 2,368 small-cell lung cancer cases and, found that individuals in occupations such as carpentry, woodworking, sawmill operations, and construction i.e. people exposed to wood dust face a 41% higher risk (RR = 1.41, 95% CI 1.11–1.80). The study results shown suggested a consistent association across different research (I^2 = 40%) [71]. A study conducted on non-smoking Chinese women found that increased exposure to cooking fumes overtime increases the chances of developing lung cancer, the risk of which was reduced up to 50% when using fume extractors while cooking [72]. Associations have also been made between occupational benzene exposure and different types of lung cancer even after controlling for smoking status and some other factors [73]. Polycyclic aromatic hydrocarbons (PAH) a common occupational exposure among chefs, firefighters, asphalt workers, and petroleum refinery worker, was found to have a positive association with lung cancer, especially small-cell and squamous lung cancers, despite accounting for smoking [74]. Men with occupational exposure to chromium (VI) and nickel showed an increased risk of lung cancer across all smoking statuses, including never, former, and current smokers. Overall, even at relatively low cumulative exposure levels, chromium (VI) and nickel were strongly associated with higher odds ratios for lung cancer, with the risk being particularly evident in men [75].

Genetic and molecular factors relating to small-cell lung cancer in never-smokers

Small-cell cancer of the lungs is largely believed to be due to smoking and while this is true there is evidence suggesting genetic associations as well, with inheritance possibly playing a role, this could potentially lead to targeted therapy for particular genes [76, 77]. Some molecular based treatments that have been used or have potential in the future include; immune checkpoint inhibitors which benefit some extensive-stage small-cell lung cancer patients, but immune evasion and tumor heterogeneity pose challenges. Besides this, the advancements in single-cell analysis, liquid biopsies, and new immunotherapy targets like DLL3 and TROP2 show promise. The ADRIATIC trial and tarlatamab approval mark key progress, with future research focusing on overcoming resistance [78]. In EGFR-mutant lung adenocarcinomas, especially in non-smokers, RB1 inactivation plays a crucial role in small-cell lung cancer transformation after treatment resistance. Genetic predisposition may also contribute to small-cell lung cancer development in some non-smokers [79]. A study found that in EGFR-mutant lung cancer, small cell lung cancer transformation occurred after a median of 17 months, with TP53 (68%) and RB1 (36%) as the most common mutations. Platinum-etoposide was the main treatment (median progression-free survival of 3.5 months), while anlotinib showed better efficacy (6.2 months) [80]. Similar to above there are a number of studies with similar genetic relations and therapeutic measures indicated for small-cell lung cancer [81-83].

DIAGNOSIS, MANAGEMENT AND PREVENTION

Diagnostic and screen challenges relating to small-cell lung cancer in never-smokers

It is suggested that never-smoking lung cancer patients may have a higher death rate; since smoking is the major risk factor for lung cancer those patients who are not engaged in smoking habits tend to undergo less diagnostic investigation, this lack of investigation in particular could possibly play a role in the higher postulated death rate [84]. Most current methods of diagnosis detect lung cancer at an advanced stage, and while early detection of small-cell lung cancer would improve prognosis there is a lack of reliable screening methods. Currently researchers suggest that sputum, blood and urine biomarkers as well as PCR, and other molecular biology-based techniques could possibly help detect lung cancer earlier, including in never-smokers [85]. Lung cancer screening is usually risk-based, meaning never-smokers are often excluded due to their lower risk. However, some never-smokers still develop lung cancer, raising concerns about when and how to screen them. Clear guidelines are needed to balance screening benefits and risks while ensuring those at increasing risk get timely diagnosis. Better information and awareness can help prevent delays in seeking medical care [86]. Some literature has even suggested that low-dose CT which is a common screening tool for lung cancer among smokers may also derive some benefits when conducted among never-smokers [87]. Lung cancer screening using low-dose CT has been proven to reduce mortality and is mainly targeted at smokers. Never-smokers are generally excluded due to their lower risk, as unnecessary testing could lead to harm from unnecessary procedures. However, ongoing research aims to refine risk assessment in never-smokers to determine if and when screening might be beneficial, ensuring early detection without excessive risks [88].

Prevention and public health strategies

1. Occupational exposure prevention

Methods for the prevention of exposure to occupational hazards include measures such as proper ventilation, protective gear, regular monitoring, and worker training. Along with this safety regulations, bioaerosol control, and hazard detection technologies also help reduce risk of exposure [89]. Preventing radon exposure requires clear risk communication, public awareness programs, and multidisciplinary collaboration, including psychology experts, to overcome biases that minimize radon risk. Effective strategies involve structured campaigns, continuous monitoring, and improved public education on radon's link to lung cancer, avoiding misinformation and apathy [90]. A great example of air pollution prevent is China's Air Pollution Prevention and Control Action Plan (APPCAP) implemented in 2013 which aimed to cut PM2.5 levels through stricter regulations, monitoring, and public awareness. Progress included fewer haze days and less fine particle growth, but rising ozone remains a challenge. Real-time monitoring helps protect health, but district-level strategies are needed for better prevention [91]. Research suggests a possible gap in knowledge in regards to second-hand smoke and its risks, prevention can be improved with educational measures to improve public knowledge on the matter [92]. Asbestos exposure is prevented through site isolation, dust suppression, ventilation, and proper personal protective equipment (PPE) use. Regulations from Occupational Safety and Health Administration (OSHA) and the European Union (EU) require exposure monitoring, training, and strict hygiene measures. Effective protection depends on correct donning, doffing, and fit-testing of PPE. Authorities assign protection factors (APFs) to respirators, and fiber monitoring ensures safety [93].

2. Improving public awareness

Methods to increase public awareness about risk factors involved in lung cancer among never-smokers have been postulated; for example, a multi-component citizen science approach that emphasizes inclusion, collaboration, and reciprocation can raise public awareness of air pollution by promoting behavioral changes through interactive tools like air quality quizzes, fostering community-led air sensing schemes via workshops, and conducting communication campaigns based on evidence based practices [94, 95]. The general consensus is that there is still a lack of appropriate knowledge regarding air pollution among the general population [96]. In regards to second-hand smoke there is a need of increasing awareness among peers of current smokers as they are at increased risk of exposure [97]. It has been suggested that knowledge on radon exposure may vary between different communities and ethnic groups, which emphasizes the need to successfully identify these groups in particular and provide adequate communication. [98]. A study conducted on risk perception of radon exposure found most participants (73%) had heard of radon, mainly from school/university (55%), but misconceptions existed, especially among those with lower education. While 95% recognized radon as harmful, 71% were not personally worried, and 60% didn't know if they lived in a high-risk area. Trust in authorities was low (47% had very little confidence), with lower-educated individuals showing more trust than higher-educated ones. Education influenced risk perception, as those who learned about radon in school were less worried than those who learned from the internet. Improved risk communication and collaboration between experts and the public are crucial for radon mitigation [99]. Similar to the above risk factors, widespread public awareness of asbestos dangers, health rights, and the advantages of an asbestos-free nation can strengthen advocacy efforts and drive political commitment toward a complete ban [100].

CONCLUSION

Small-cell lung cancer among never-smokers is a rising issue, with research suggesting distinctive risk factors, genetic variations, and possible disparities in diagnosis and prognosis. Even though smoking is the leading cause of small-cell lung cancer, environmental and occupational factors like air pollution, radon, asbestos, and second-hand smoke contribute notably in never-smokers. Genetic predispositions and molecular changes, especially in EGFR-mutant lung cancer, add complexity to the scenario of this disease. Even with the progress in lung cancer research, never-smokers continue to face screening and diagnostic difficulties, frequently being left out of regular lung cancer screenings because of their perceived lower risk. The absence of early detection strategies is partly responsible for worse outcomes, highlighting the necessity for enhanced risk assessment measures. Low-dose CT scans and biomarker-based diagnostic strategies are promising, but more work is needed to optimize screening recommendations and weigh against possible risks the advantages of early detection. Prevention programs must address decreases in occupational and environmental exposures, enhance workplace protections, and increase public awareness. Public education programs aimed at high-risk groups such as never-smokers can correct knowledge gaps and encourage early medical treatment. The call for greater regulation of air pollution, radon exposure, and asbestos continues to be necessary, especially among low- and middle-income countries. With time, as the incidence of lung cancer among never-smokers increases, specialized research, enhanced screening practices, and precision therapies will be paramount to treating this unique subset of small-cell lung cancer patients. An interdisciplinary effort between public health campaigns, regulatory guidelines, and advances in precision medicine can maximize early detection, enhance treatment outcomes, and eventually minimize the disease burden of lung cancer among never-smokers.

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