Proposals for the prevention of lung cancer in the health system of Mexico

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Abstract
The management of lung cancer is challenging. However, nowadays the main goal is to achieve a significant overall survival accompanied by a good quality of life. Because smoking is associated with up to 71% of cancer deaths, the first policy that should be established is one that promotes strategies for healthy lifestyles by providing information about lung cancer, risk factors, protection factors, and precautionary data. Furthermore, an effective screening method that would allow early diagnosis should be established. Following diagnosis, the patient should be genotyped to identify predisposing mutations to give personalized medicine to the patient. The health system policies should include information that affects the health of the population and simultaneously allows for early diagnoses, resulting in a higher survival rate.

Keywords: carcinoma; non-small-cell lung; public health, primary prevention; secondary prevention; early diagnosis

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Resumen
El manejo del cáncer de pulmón es un reto que tiene como objetivo una supervivencia global significativa que se vea rodeada de una buena calidad de vida. Si se considera que el tabaquismo está asociado hasta con 71% de las muertes por cáncer, la primera política que debe establecerse es la de proporcionar información sobre el cáncer de pulmón, factores de riesgo, factores de protección y datos de alarma mediante una estrategia de salud de línea de vida, además del establecimiento de un método de tamizaje efectivo que permita un diagnóstico temprano. Después del diagnóstico, debe realizarse una genotipificación para identificar mutaciones sensibles y para proporcionar un tratamiento personalizado al paciente. Las políticas del sistema de salud deben incluir información para que la población incida en su salud y también se puedan realizar diagnósticos tempranos que permitan una mayor supervivencia.

Palabras clave: carcinoma de pulmón de células no pequeñas; salud pública; prevención primaria; diagnóstico precoz

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Lung cancer is a prevalent disease in the modern world. Its management currently poses a challenge because it aims for a higher overall survival in the patients through an effective course of treatment that allows the patient to maintain a good quality of life. Confronting this challenge means finding the best comprehensive treatment, which involves accessibility to doctors, timely diagnosis, and, from a preventative perspective, the existence of policies that inform the population about this disease.

In 2012, the incidence of lung cancer was reported at 1.8 million patients.[1] The most frequently observed variety is non-small cell lung cancer, which accounts for up to 85% of the cases. The population most highly affected by lung cancer is males in their sixties. The primary preventable etiological factor related to lung cancer is smoking.[2]

Smoking represents 22% of cancer deaths worldwide and approximately 71% of lung cancer deaths.[2, 3] The risk of developing lung cancer for a pack-a-day smoker who has been smoking for 40 years is 20 times higher than the risk for someone who has never smoked.

It was previously mentioned that men are the most affected, but during the last 30 years, the number of lung cancer cases in women has proportionally increased. Together, up to 41% of these patients present exposure to firewood smoke, a product of cooking with firewood, as a risk factor. Although this is a factor in Mexico, with approximately 25 to 28 million Mexicans (primarily women) exposed to firewood smoke, it is not a factor that is observed in industrialized nations.[4, 5]

There are other factors that make up this multifaceted ailment. These include exposure to secondhand smoke (SHS), occupational exposure to asbestos, and exposure to radiation. Genetically, patients who have first-degree relatives with lung cancer have an increased risk of contracting this illness at an early age.[6, 7] We emphasize this last item because of the existence of mutations that are markers of bad prognosis. One of these mutations is the Kirsten rat sarcoma viral oncogene homolog (KRAS). The presence of epidermal growth factor receptor (EGFR) gene mutations in Latin Americans, however, is associated with a higher survival rate. This information, genotyping, and the subsequent identification of predisposing mutations allows for the establishment of a directed treatment.[8, 9]

There is a broad framework for dealing with lung cancer; however, given the background discussed, the first proposal should focus on the prevention of lung cancer in the Mexican population. The primary prevention tactic is focused on the reduction of lung cancer incidence by avoiding the beginning of tobacco consumption in the general population, promoting tobacco abstinence in the smoker population, and avoiding exposure to SHS.

It is alarming that 21.7% of the Mexican population between the ages of 12 and 65 are active smokers and that the average age of beginning tobacco consumption is 14.1 years old.[10] It is also important to consider that 30.2% of the non-smoking population encounters exposure to SHS. The amount of smokers and people exposed to SHS combined includes more than 30 million Mexicans. It is in this population and in recently diagnosed patients where measures to promote smoking cessation should be taken. Therefore, information and lung cancer prevention and control strategies must be provided to the different age groups through the lifeline strategy. In addition, the diffusion of information via communication mediums such as national pamphlets should be continued. All of these efforts are aimed towards the objective of providing information that promotes a life without tobacco, encourages exercise, and shows the harmful effects of smoking, all while showing the benefits of a healthy lifestyle, promoting the avoidance of smoking and, as a result, preventing the continuous rise of tobacco use in the youth population.

Avoiding smoking decreases the risk of developing lung cancer by more than 90% after 30 years of abstinence. If a smoking habit stops before 30 years of age, the mortality from lung cancer decreases to values similar to those for the population that never smoked.[11-14] A tobacco addicted patient requires comprehensive management with cognitive behavioral therapy and, at times, medication management. This strategy allows the patient to revert his or her learning of smoking as a coping mechanism and modifies what the smoker thinks and does.[15] Available medications for controlling tobacco addiction allow for 70% of consumers to quit smoking. These include nicotine replacement through patches or chewing gum,[16] bupropion,[17] and varenicicline tartrate.[18]

However, because SHS increases the risk of lung cancer to 20-30% for non-smoking individuals who live with smokers,[19] beginning in 2003, the WHO adopted the Framework Convention on Tobacco Control. Mexico signed and ratified this agreement and passed the General Law for the Control of Tobacco and the Law of Protection for the Health of Non-Smokers in Mexico City in 2008, prohibiting smoking in all public places.[20] It is now necessary to maintain these policies initiated in the specific program against tobacco addiction that was established in 1991.[21] Helping non-smokers avoid exposure to SHS is essential to protecting the health of the population.

It is also necessary to prevent the population's exposure to pollution from the incomplete combustion

of fossil fuels, which heightens the risk of developing lung cancer. This is particularly true for the exposure to firewood smoke, which is a problem that may be directly combated.

We believe that complying with the primary measures of prevention will allow for a decrease in the incidence of this disease and guarantee better health care for Mexicans by encouraging self-care and health promotion. The maintenance of policies against exposure to SHS, avoiding the use of electronic cigarettes, following measures of environmental care, avoiding cooking with wood in enclosed areas, and using appropriate protection from and limiting the exposure to unnecessary radiation are some of the measures that should be spread to the population to decrease the prevalence of lung cancer.

The next point of suggestion is regarding the establishment of early detection through a secondary prevention or screening program. The objective of this program is to reduce NSCLC mortality by identifying the cases in early clinical stages.

The high mortality rate observed in lung cancer is a result of most diagnoses occurring in late stages of the disease, generating a five-year survival rate of only 16.3%. Additionally, late diagnosis increases the cost of care for patients at advanced stages of disease, which are 5 to 10 times greater than for patients who are provided treatment at early stages.[22]

Screening is an intervention intended to benefit the patient from a diagnosis in early stages of the disease and is conducted on asymptomatic and healthy individuals. According to the results of the United States National Lung Screening Trial (NLST), lung computed tomography at low doses of radiation can detect lung cancer in the initial stages and can reduce the risk of death from this disease. A 20% reduction in lung cancer deaths was observed in people who were submitted to an annual screening with CT compared to people at risk for lung cancer who received chest x-rays (males and females 55-75 years of age who smoked the equivalent of one pack of cigarettes a day for 30 years).

Irrefutably, before the establishment of screenings, we are confronted with the issue of defining which population we can conduct a study on and which population might benefit. Keeping this in mind, in accordance with the results of various studies and through the previous experience of patients of the National Institute of Oncology, the sample population should include smokers between the ages of 55 and 75 with a smoking index (SI) of 30 packs per year or who have stopped smoking within the past 15 years. The sample should also include women with prolonged exposure (20 years) to firewood smoke. The sample population would be located in an opportunistic area, have undergone previous evaluation, and would preferably include a group of smokers with an SI of 20 to 29 pack-years.[23] With long-term studies, there would clearly be an increase in the number of individuals who possibly would increase the cost and the risk of diagnostic procedures such as bronchoscopy examinations. However, we consider that it is important to provide the entire population with the opportunity to receive an early diagnosis.

The viability of providing this opportunity to the entire population in Mexico seems well out of reach, but many projects have begun with difficult goals. We propose to perform the identification of individuals at risk at a local/regional level. These individuals may then be referred to specialized centers specific to their state where this strategy can be enacted (CT with low levels of radiation). This action will consequently allow for the evaluation of the effect of this strategy and, furthermore, will provide a better control of the number of patients at risk and the effects of early diagnosis and treatment.

Taking into account the relative frequency at which lung cancer is identified in early stages during a detection study, there is interest in the application of minimally invasive techniques for the resections of small tumors. This strategy should also involve an institutional program that includes the availability of a multidisciplinary program, careful selection of the participants with continuous education and assessment, smoking cessation, control of the quality of the tomographic studies, a process of standardized interpretation, an intervention algorithm, data records, and video-assisted thoracic surgery.

Regarding genotyping, this proposed screening can be useful because a sample of tumoral tissue helps to identify the presence or absence of either predisposed or targeted mutations. This is how genetic alterations currently form part of the arsenal for personalized medicine in non-small cell lung cancer. The alterations become therapeutic targets based on the presence of coding mutations.[24,25]

Up to 50% of non-small cell lung cancers have coding mutations with possible therapeutic targets.[26] The most frequently mutated genes in adenocarcinoma of the lung are the EGFR and KRAS genes.[27] Other mutations include rearrangements of the anaplastic lymphoma kinase (ALK), vascular endothelial growth factor (VEGF) and its receptor (VEGFR), BRAF, ROS1, and mesenchymal-endothelial transition factor (MET) genes, as well as the amplification of the human epidermal growth factor receptor 2 (HER2) and a variety of other molecules that regulate different signal transduction pathways.

With the presence of some coding mutations constituting therapeutic targets, the implementation of specific treatment allows for an improvement in the survival and quality of life of the patients. For example, when mutations in the tyrosine kinase (TK) domain of EGFR are present, tyrosine kinase inhibitor (TKI) drugs are used.[28-30] The identification of frequent EGFR mutations assures the initiation of a therapeutic approach with TKIs, whereas patients presenting less frequent mutations would begin with a platinum-based treatment.[31]

In addition to the mutations described above, there are also mutations in exon 20 (T790M / L858R, G719, and L861Q) that have a *de novo* or acquired resistance to TKIs.

Another therapeutic target is the identification of an inversion on the short arm of chromosome 2, inv (2) (p21-p23), which results in an N-terminal fusion of protein 4, similar to the fusion of echinoderm microtubule-associated protein-like 4 (EML4) with the ALK domain.[32-35] The rearrangement of ALK is nearly always found in solid subtype adenocarcinoma with signet-ring cells. This subtype corresponds to younger patients and non-smokers or occasional smokers (10 packs per year), although not all of the patients present these clinical characteristics. The presence of a rearrangement of the ALK gene in adenocarcinomas of the lung is the best predictor of response to crizotinib, a TKI-ALK. The response rates of crizotinib are as high as 65%, and its progression-free survival rate is 7.7 compared to three months of chemotherapy on a locally advanced or metastatic illness.[36]

The role of non-small cell lung cancer in Mexico represents a challenge, as does any other health-related topic in the country. With the current advances, however, there is hope in generating changes that cause improvements for the population. The proposals suggested in this paper are intended to be a starting point to provoke debate within health administrations, researchers, and other parties of interest. In any case, these ideas underlie the necessity for a multidisciplinary approach that establishes assumptions for the management of lung cancer in Mexico.

The process must begin with the implementation of accessible screening methods pertinent to the Mexican population, along with resource optimization. These steps will ensure early diagnosis and better results for the patients with non-small cell lung cancer.

Another fundamental aspect is the education of the patient, or more accurately, the population. The distribution of all information regarding preventable risk factors, which include smoking, work related exposure, or daily firewood smoke exposure; will allow the public to be more informed. With this education, preventative measures may be taken to improve the Mexican population's awareness of their health and commit to changes or actions to promote healthy lifestyles.

With the occurrence of worldwide advances, it is important that Mexico be integrated into the studies that evaluate the effects of medications approved by prestigious foreign entities such as the U.S. Food and Drug Administration and the European Medicines Agency. Bioequivalence studies and the evaluation of these drugs in the Mexican population must be conducted.

The view that is presented shows that it is imperative to continue studying and applying the acquired knowledge to develop health policies that are applicable to Mexicans. It also encourages the search for better treatments that provide prolonged survival with a good quality of life for the patients.

New developing fields, which include immunotherapy and targeted therapies in non-small cell lung cancer, will most likely provide more information regarding the knowledge of the ailment in the population and will influence the survival rate of the patients. To properly evaluate these fields, the use of the techniques must first be generalized, and more research must be conducted in these areas. When this is accomplished, these treatments may also be used to make a difference in the patient's overall survival and quality of life.

The field of non-small cell lung cancer is currently an area in continuous development. It is indispensable to continue working to not only obtain information about the disease but also develop means for better care of the patients. This advancement will cause a change in the Mexican population because the application of a multimodal approach will provide the best treatment to the patients. The application of new therapeutic approaches, together with genetic studies and the use of personalized medicine, is expected to positively affect the survival rate of non-small cell lung cancer patients in Mexico.

Declaration of conflict of interests. The authors declare that they have no conflict of interests.

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