Editorial Commentary

Current and future perspectives in lung cancer prevention

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Received: 31 June 2020. Accepted: 23 July 2020; Published: 30 September 2020.
doi: 10.21037/pcm-20-31
View this article at: http://dx.doi.org/10.21037/pcm-20-31

Tobacco smoking and lung cancer

Smoking is one of the leading causes of morbidity and mortality worldwide. Tobacco smoke contains thousands of different heterogeneous substances, dozens of them classified as carcinogenic for humans, including tobacco-specific nitrosamines (TSNAs), metals and polycyclic aromatic hydrocarbons, among others. Deleterious effects of tobacco consumption occur not only in active smokers, but also in people passively exposed to secondhand and thirdhand smoke, the latter including children (1).

There are diverse disorders associated with tobacco smoking, including cardiovascular and respiratory conditions, and cancer in multiple sites and organs (e.g., urinary bladder, stomach, lung). Lung cancer is one of the most concerning disorders associated with smoking and the first cause of cancer mortality worldwide. In 2018, an estimated 1.76 million people died of lung cancer, a higher figure than the sum of the second and third top causes of cancer-specific mortality (i.e., colorectal and stomach) (2). Lung cancer shows an overall 5-year survival rate from diagnosis of around 15–20% (3), one of the lowest among all types of cancer, result of a frequent late diagnosis in advanced stages, when the prognosis is poorer, due to the commonly unspecific initial symptoms. This survival rate has remained almost invariable for years.

Around 80% of the cases of lung cancer are associated with tobacco consumption (4), while the second leading cause of lung cancer incidence, radon exposure, is linked to around 3–14% of all lung cancers (5). Remarkably, there is an important combined effect between tobacco smoking and radon exposure.

Tobacco smoking, and hence lung cancer, have been historically associated with the masculine gender. However, there is nowadays a worrying increase of lung cancer incidence and mortality in women in multiple countries, consequence of the incorporation of women to tobacco smoking in the last decades due to sociocultural changes. Such is the increase in lung cancer incidence in women that lung cancer mortality in this group is going to surpass breast cancer mortality in many countries, while in others this overtake has already occurred (6). Besides, in some countries, the proportion of smoking attributable mortality is now higher in women than in men. This situation was perfectly depicted by Lopez *et al.* back in 1994 in their well-known descriptive model of the cigarette epidemic in developed countries (7). This model is based on four stages, defined by the prevalence of tobacco consumption and the smoking-attributable mortality in men and women at the national level. The curve of the prevalence of tobacco consumption is delayed in women around 2–3 decades with respect to the curve in men. Consequently, and also associated with the pathogenesis of lung cancer, there is also a similar lag in the curve of the proportion of lung-cancer mortality attributable to tobacco consumption between men and women (8). In some countries, well into stage four, where the proportion of smoking-attributable mortality was on the rise in women during the last years and decreasing in men, the crossover of the curves of mortality has almost or actually occurred, as reflected in the updated version of the descriptive model of Lopez *et al.* (9).

On the tobacco harm reduction strategy

While in several developing countries the rates of cigarette

consumption are still high and on the rise, a progressive social denormalization of tobacco use has occurred in many developed countries, also supported by legislative modifications taken by policymakers. This process has made the industry shift its production towards more appealing and modern devices, devices that include, but are not limited to, Heated Tobacco Products (e.g., IQOS) and electronic nicotine, and non-nicotine, delivery systems (e.g., electronic cigarettes).

Taking advantage of this marketing adaptation, the tobacco industry (and related stakeholders) promoted the Tobacco Harm Reduction strategy, arguing that the impact on health of the use of these products would be lower than with the traditional (combustible) cigarettes. Nevertheless, evidence on the efficacy and long-term health outcomes, both positive and negative, of these devices is still sparse (10), and the prevalence of dual use (i.e., combustible tobacco along with a new device) is high. Unsurprisingly, it has been observed that "evidence" supporting a beneficial use of electronic cigarettes is more often affected by conflicts of interest (11). It is relevant to remark that, in this context, the tobacco industry is taking advantage of the loopholes in the legislation in different countries to reach a wider potential market, specially youngsters, showing no real interest in the improvement of public health.

Further research is needed to fully understand the risk-benefit balance of these products. However, while they could eventually be prescribed to quit tobacco smoking if net benefits in health were observed in well-designed studies, by no means can they be a gateway to nicotine for current non-smokers, as observed in the epidemic of JUUL in teenagers in the United States.

Lung cancer prevention activities

Prevention of lung cancer is based on primary and secondary prevention activities. Primary prevention activities are aimed at smoking cessation and non-initiation campaigns, which rely mainly on tobacco control policies. Globally, tobacco control foundations are set on the World Health Organization Framework Convention on Tobacco Control, which came into force in 2005, and the MPOWER measures proposed thereafter.

The implementation of tobacco control policies is associated with different health outcomes (12,13), included negatively with the high risk of lung cancer in the European Union (EU) (14). In this scenario, a systematic assessment of the implementation of these policies gains importance. In Europe, the implementation of tobacco control policies at the national level is quantified every three years since 2005 with the Tobacco Control Scale (15), a tool developed by Luk Joossens and Martin Raw. This scale quantifies from 0 (worst) to 100 (best) the implementation of six cost-effective tobacco control policies proposed by the World Bank, including: price increases through higher taxes on cigarettes and other tobacco products; bans/restrictions on smoking in public and work places; better consumer information, including public information campaigns, media coverage, and publicising research findings; comprehensive bans on the advertising and promotion of all tobacco products, logos and brand names; large, direct health warning labels on cigarette boxes and other tobacco products; and treatment to help dependent smokers stop, including increased access to medications. Although the most cost-effective tobacco control policy is taxing tobacco products, there is a combined effect in the implementation of different tobacco control policies, hence a comprehensive approach is preferred.

At the secondary level, preventive activities correspond to lung cancer screening programs. While chest X-ray with or without sputum cytology was found in the past to be ineffective in the reduction of lung cancer mortality, multiple trials have been conducted worldwide in the last decades, and others are still on course, to assess the efficacy of the low-dose computed tomography (LDCT) as screening tool. The most important trials, as far as the statistical power is concerned, were the US National Lung Screening Trial (NLST) (16), in which diametric assessment was applied, and the Nederlands-Leuvens Longkanker Screening Onderzoek (NELSON) (Dutch-Belgian Lung Cancer Screening trial) (17), applying volumetric assessment.

Results from the NLST trial (16) published in 2011, showed a 20.0% reduction in lung cancer mortality and a 6.7% reduction in all-cause mortality in the arm screened with LDCT in comparison to the arm screened with chest X-Ray. These results prompted a positive recommendation from the US Preventive Services Task Force for the implementation of lung cancer screening programs in the US for adult current and former smokers with a high cumulative history of tobacco consumption. As a result, lung-cancer screening in community settings is ongoing in the US, although uptake is so far low.

In early 2020, the results of the NELSON trial (17) also showed a statistically significant reduction of 24.0% in lung cancer mortality in the screening group versus the control group, in which no intervention was performed.

Remarkably, differences in all-cause mortality were not observed. Based on these results, and as in the US, different scientific societies (e.g., European Respiratory Society) and groups of experts in Europe have advocated for the implementation of selective lung cancer screening programs, since lung-cancer mortality reduction in the intervention arm was clearly associated with an earlier detection of carcinomas in initial stages, as shown in the NLST trial. Nevertheless, there is still controversy, and debate is ongoing in the scientific community (18,19), since the risk-benefit balance must still be fully assessed due to the high false-positive rates reported in the trials (and the psychosocial consequences associated) and other detrimental effects associated with screening, such as overdiagnosis or exposure to radiation. As of today, the only officially recommended cancer-screening programs in the EU are breast, colorectal and cervical.

Regarding the cost-effectiveness of lung cancer screening programs, it has been estimated that for each lung cancer screening, 20 smoking cessation activities could be carried out. However, models for different countries in diverse scenarios indicate that lung-cancer screening programs may be cost-effective (20).

The optimization of screening programs, meaning maximizing the benefits while reducing harms and costs, requires sound designs, such as an optimal interval between screenings (which has not been set so far for lung-cancer screening) and an appropriate selection of high-risk participants. For the latter, two main approaches have been considered. On the one hand, what has been defined elsewhere as simplified elegibility criteria (21), applied in the main lung cancer screening trials. These criteria are based on the variables cumulative history of tobacco consumption and age, of which information are easy to obtain even outside the clinical trial context. Although these two variables explain most of the risk of lung cancer, it has been observed in cancer registries from the US that many cases of lung cancer did not meet NLST criteria (22). Besides, around 25% of cases of lung cancer worldwide are found in never smokers (up to 53% in women). This means that there are other exposures (e.g., asbestos) and prognostic factors (e.g., comorbidities, such as emphysema) with an important impact on lung cancer incidence and mortality. These variables, among others, have been incorporated into diverse risk prediction models (23), which estimate the individual probability of incidence or mortality of lung cancer. Also, and to avoid self-reporting bias associated with tobacco consumption, the concentrations of TSNAs of current smokers have been proposed to be incorporated in the prediction models, since the concentrations of certain TSNAs and cotinine, the main metabolite of nicotine, have been found to be associated with the high-risk of lung cancer (González-Marrón A, 2020, unpublished data).

Taking advantage of the teachable moment

Smoking cessation is, without a doubt, the most effective way to reduce lung cancer incidence. Such is the importance of quitting that within the shared decision-making process required to receive coverage by the Center for Medicare and Medicaid Services in the US for participating in a lung cancer screening, counsel to quit and providing information on cessation strategies are pivotal conditions (24). Besides, benefits of quitting go beyond the diagnosis of lung cancer, and even after a diagnosis in early stages, smoking cessation seems to improve prognosis and is associated with better performance status.

Interestingly, cancer screening programs have been described as a teachable moment (25), a timeframe in which participants are more prone to adopt healthy habits due to an increased risk perception. While smoking cessation should be an integral part of lung cancer screening, the *teachable moment* applies not only for this setting, but also for other population-based screening programs. This means that breast, colorectal and cervical cancer screenings may offer an opportunity to counsel on quitting smoking and modifying other habits (e.g., encourage physical activity, avoid harmful use of alcohol) towards a healthier lifestyle. Regarding quitting smoking, the implementation of the *teachable moment* would be clearly beneficial in cervical cancer screenings, since the majority of participants are not still at high risk of lung cancer due to lower cumulative tobacco consumption.

Conclusions

Lung cancer poses a high burden of morbidity and mortality and tremendous costs to the health systems globally. While smoking cessation should be the basis to minimize the grievous consequences of this public health threat, results arising from the main lung cancer screening trials may show an opportunity to fight this condition from the secondary level. Further efforts from different actors, from policymakers to stakeholders, and healthcare professionals and researchers, will be needed to put an end to this dire condition.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Precision Cancer Medicine*. The article did not undergo external peer review.

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/pcm-20-31). The authors have no conflicts of interest to declare.

Ethical statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Díez-Izquierdo A, Cassanello-Peñarroya P, Lidón-Moyano C, et al. Update on Thirdhand Smoke: A Comprehensive Systematic Review. Environ Res 2018;167:341-71.
2. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68:394-424.
3. De Angelis R, Sant M, Coleman MP, et al. Cancer Survival in Europe 1999-2007 by Country and Age: Results of EUROCARE--5-a Population-Based Study Lancet Oncol 2014;15:23-34.
4. Centers for Disease Control and Prevention (CDC). Annual smoking-attributable mortality, years of potential life lost, and economic costs--United States, 1995-1999 MMWR Morb Mortal Wkly Rep 2002;51:300-3.
5. World Health Organization. WHO Handbook on Indoor Radon: A Public Health Perspective. WHO Press, Geneva, 2009.
6. Martín-Sánchez JC, Lunet N, González-Marrón A, et al. Projections in breast and lung cancer mortality among women: A Bayesian analysis of 52 countries worldwide. Cancer Res 2018;78:4436-42.
7. Lopez AD, Collishaw NE, Piha T. A descriptive model of the cigarette epidemic in developed countries. Tob Control 1994;3:242-7.
8. Martín-Sánchez JC, Bilal U, Clèries R, et al. Modelling Lung Cancer Mortality Rates From Smoking Prevalence: Fill in the Gap. Cancer Epidemiol 2017;49:19-23.
9. Thun M, Peto R, Boreham J, et al. Stages of the cigarette epidemic on entering its second century. Tob Control 2012;21:96-101.
10. Worku D, Worku E. A narrative review evaluating the safety and efficacy of e-cigarettes as a newly marketed smoking cessation tool. SAGE Open Med 2019;7:2050312119871405.
11. Martínez C, Fu M, Galán I, et al. Conflicts of interest in research on electronic cigarettes. Tob Induc Dis 2018;16:28.
12. Gallus S, Lugo A, La Vecchia C, et al. Pricing Policies And Control of Tobacco in Europe (PPACTE) project: cross-national comparison of smoking prevalence in 18 European countries. Eur J Cancer Prev 2014;23:177-85.
13. Feliu A, Filippidis FT, Joossens L, et al. Impact of tobacco control policies on smoking prevalence and quit ratios in 27 European Union countries from 2006 to 2014. Tob Control 2019;28:101-9.
14. González-Marrón A, Martín-Sánchez JC, Miró Q, et al. Relation between tobacco control policies and population at high risk of lung cancer in the European Union. Environ Res 2019;179:108594.
15. Joossens L, Raw M. The Tobacco Control Scale: A New Scale to Measure Country Activity. Tob Control 2006;15:247-53.
16. Aberle DR, Adams AM, Berg CD, et al. Reduced Lung-Cancer Mortality with Low-Dose Computed Tomographic Screening. N Engl J Med 2011;365:395-409.
17. de Koning HJ, van der Aalst CM, de Jong PA, et al. Reduced Lung-Cancer Mortality with Volume CT Screening in a Randomized Trial. N Engl J Med 2020;382:503-13.
18. Ruano-Ravina A, Pérez-Ríos M, Casàn-Clará P, et al. Low-dose CT for lung cancer screening. Lancet Oncol 2018;19:e131-2.
19. Field JK, Heuvelmans MA, Devaraj A, et al. Low-dose CT

for lung cancer screening - Authors' reply. Lancet Oncol 2018;19:e135-6.
20. Puggina A, Broumas A, Ricciardi W, et al. Cost-effectiveness of screening for lung cancer with low-dose computed tomography: a systematic literature review. Eur J Public Health 2016;26:168-75.
21. Kaaks R, Hüsing A, Fortner RT. Selecting high-risk individuals for lung cancer screening; the use of risk prediction models vs. simplified eligibility criteria. Ann Transl Med 2017;5:406.
22. Pinsky PF, Berg CD. Applying the National Lung Screening Trial eligibility criteria to the US population: what percent of the population and of incident lung cancers would be covered? J Med Screen 2012;19:154-6.
23. Gray EP, Teare MD, Stevens J, et al. Risk Prediction Models for Lung Cancer: A Systematic Review. Clin Lung Cancer 2016;17:95-106.
24. Jensen TS, Chin J, Ashby L, et al. Decision memo for screening for lung cancer with low dose computed tomography (LDCT) (CAG-00439N). Centers for Medicare & Medicaid Services [published 5 Feb 2015, accessed 11 Jun 2020]. Available online: https://www.cms.gov/medicare-coverage-database/details/nca-decision-memo.aspx?NCAId=274
25. Senore C, Giordano L, Bellisario C, et al. Population based cancer screening programmes as a teachable moment for primary prevention interventions. A review of the literature. Front Oncol 2012;2:45.

doi: 10.21037/pcm-20-31
Cite this article as: González-Marrón A, Martín-Sánchez JC, Martínez-Sánchez JM. Current and future perspectives in lung cancer prevention. Precis Cancer Med 2020;3:18.