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Early Life Exposure to Tobacco Smoke and Lung Cancer in Adulthood

To the Editor:

A significant and well-constructed United Kingdom Biobank prospective cohort study named "In Utero and Childhood/Adolescence Exposure to Tobacco Smoke, Genetic Risk, and Lung Cancer Incidence and Mortality in Adulthood" was recently published in the *Journal* (1). He and colleagues have clearly identified that exposure to tobacco smoke in early life, with careful and quantifiable consideration of lung polygenic cancer risk via genome-wide association studies, was significantly associated with risks of lung cancer incidence and mortality in adulthood (1). This manuscript undoubtedly provides important information on lung cancer prevention in people's early life while urging a more rapid and powerful need for tobacco control among pregnant couples, children, and adolescents. And we want to take this opportunity to share some additional thoughts about this elaborate work.

First, as the authors declared in Methods and study limitations, the definition of early life tobacco exposure was self-reported and retrospectively collected after a long period of time in which recall bias seemed to be huge and inevitable. To reduce this kind of bias, we suggested the authors could perhaps consider using measurable biomarkers, like serum cotinine, to define tobacco smoke exposure, that was more precise and stable (2). And defining smoking exposure via serum cotinine made it possible to not only distinguish secondhand smoke and active smoke but also quantify the amount of tobacco smoke exposure to assess its dose–dependent relationship with lung cancer incidence and mortality (3). If serum cotinine was not available in this cohort, the authors could also take the smoking status of the father during the children's early life into consideration because the impact of active smoke and secondhand smoke on cancer might not be the same.

Furthermore, we thought the mechanism behind the impact of early life tobacco smoke exposure on lung cancer development merited further discussion. Though not fully understood, untimely telomere length reduction could play an unfavorable role in cancer development. Whiteman and colleagues reported that maternal smoking during pregnancy was associated with shortened fetal telomere length, leading to early intrauterine programming for accelerated aging (4). Another HELIX (Human Early Life Exposome) cohort study revealed that both active smoke and secondhand smoke during pregnancy could accelerate telomere shortening in children (5), which might be strong risk factors for lung cancer risk and mortality. And many researchers showed that tobacco smoke induced abnormal oxidative stress followed by DNA breakage, resulting in the reduction of telomere length (6). Oxidative stress, characterized as excessive exogenous and endogenous reactive oxygen species aggregation, could lead to rapid and even specific telomeric DNA damage while inhibiting protective DNA damage response and hampering DNA repair (6). Impaired telomeres could also lead to mitochondrial dysfunction via activating tumor repressor gene p53 to promote oxidative stress (6). At the same time, oxidative stress-induced inflammation with elevated inflammatory cytokines such as IL-6 and TNFα (tumor necrosis factor α) could further aggravate the telomere-shortening process and cell injury (6).

In conclusion, this work obtaining data from a prospective United Kingdom Biobank cohort illustrated a strong negative effect of early year tobacco smoke exposure on lung cancer incidence and mortality in adulthood very well, raising public attention on tobacco control from an early life stage. We thank and congratulate the authors again for their elaborate and illuminating paper. ■

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Reply to Liu and Xiong

From the Authors:

We would like to thank Nuozhou Liu and Wei Xiong for their interest and suggestions on our paper (1). They provided some unique insights into early life tobacco exposure assessment and the mechanism between early life tobacco smoke exposure on lung cancer.

Cotinine, a metabolite of nicotine, which can be measured in serum, urine, or saliva, has been considered a reliable and useful biomarker for assessing tobacco smoke exposure and evaluating the dose–response relationship between tobacco exposure and lung cancer (2, 3). Compared with the advantages of cotinine, we still need to acknowledge that self-reported smoking status may tend to underestimate true smoking prevalence (4). However, most studies have observed that self-reported estimates correlate strongly with measured cotinine concentrations and show a similar ability with urine cotinine on the assessment of tobacco-related risks of disease (4–7). More importantly, if urine cotinine could not exhibit clear superiority over self-reported smoking in the associations, measurement of cotinine concentration may not always be feasible and effective in large-scale prospective cohort studies in which the costs and benefits need to be considered (4, 6).

As for taking the smoking status of the father during children's early life into consideration, secondhand smoke exposure and environmental tobacco smoke exposure were not available in the United Kingdom Biobank, which we have already stated in our limitations.

We completely agree that the mechanisms underlying the effect of early tobacco smoke exposure on the development of lung cancer are not limited to the epigenetic alterations (8, 9), DNA damage, or chromosomal deletions (10, 11) mentioned in our paper. Shortened telomere length may also be one of the mechanisms behind the impact of early life tobacco exposure on lung cancer progression, as suggested by Xiong and colleagues. To shed light on this process, we could examine the mediating role of telomere length in the association between early life tobacco exposure and lung cancer incidence and mortality in further studies. ■

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