

Peer Review

Review of: "Vitamin D Deficiency in Smokers: A Major Risk Factor in Lung Carcinogenesis"

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This review presents an in-depth and timely exploration of the complex interplay between tobacco smoking, lung cancer pathogenesis, and vitamin D deficiency, with a particular emphasis on the molecular mechanisms that mediate this relationship. One of the key strengths of the manuscript lies in its comprehensive scope, encompassing a wide array of genetic, epigenetic, inflammatory, and signaling pathways. The narrative is thoroughly supported by recent literature and framed within the broader context of global cancer epidemiology, providing both clinical and molecular relevance.

A notable merit of this review is the detailed synthesis of data highlighting how smoking alters vitamin D metabolism and receptor expression. The linkage of VDR polymorphisms and downregulation with tobacco-related carcinogens offers valuable insight into why smokers are particularly prone to vitamin D deficiency and the downstream oncogenic consequences. This connection sets the stage for considering vitamin D not merely as a micronutrient, but as a potential modulator of cancer-related pathways.

The manuscript effectively integrates a wide range of mechanistic data, including the role of vitamin D in mitigating calcium influx, oxidative stress, inflammation, and immune suppression. The graphical elements (e.g., Figures 1–4) are conceptually appropriate and enhance the readability of the dense content. The authors demonstrate scientific rigor in connecting vitamin D's biochemical and cellular functions with key oncogenic events in smoking-induced lung carcinogenesis.

Furthermore, the discussion of mutations in genes such as TP53, KRAS, EGFR, and others is particularly insightful. By positioning vitamin D as a potential factor that influences survival or therapeutic responsiveness in patients with these mutations, the review opens meaningful avenues for personalized medicine. The section linking vitamin D to modulation of key signaling pathways (e.g., PI3K/AKT, MAPK, NF- κ B, JAK/STAT) is another highlight, showcasing vitamin D's broader cellular impact.

However, while the review is impressively thorough, it could benefit from a clearer structural segmentation. The text is currently very dense and could be improved by subdividing long sections into more distinct thematic areas (e.g., “Genetic Mutations,” “Epigenetic Modifications,” “Immune Dysregulation”). This would enhance navigability, especially for readers who wish to focus on specific subtopics.

Additionally, while the molecular pathways are extensively discussed, there is limited critical appraisal of the clinical implications or limitations of current evidence. For example, it would strengthen the review to more clearly distinguish between in vitro, animal model, and clinical trial findings. How translatable are these findings to human patients? Are there ongoing clinical studies investigating vitamin D supplementation in high-risk smokers or lung cancer cohorts?

Another opportunity for improvement involves addressing potential confounders in vitamin D research, such as dietary intake, genetic variability in vitamin D metabolism, and sunlight exposure. These variables are briefly touched upon but could be more explicitly integrated into the discussion of the observed associations. Also, while vitamin D toxicity is rare, mentioning the safety thresholds and risks of high-dose supplementation would provide a balanced perspective.

Moreover, although the authors mention the need for further research, the conclusion could benefit from a more specific set of future directions. For instance, what biomarkers could be validated to assess vitamin D's effect in smokers? What are the most promising molecular targets or patient subgroups for intervention? Incorporating such targeted recommendations would elevate the translational potential of the manuscript.

In summary, this is a scientifically rich and well-documented review that provides a valuable contribution to understanding the intersection between smoking, lung cancer, and vitamin D metabolism. Its major strength lies in the detailed mapping of molecular mechanisms and signaling pathways. To maximize its impact, the manuscript would benefit from structural refinement, more critical appraisal of clinical data, and a forward-looking perspective on research translation and public health implications.

Declarations

Potential competing interests: No potential competing interests to declare.