Vire *et al. Biomarker Research* (2025) 13:148
https://doi.org/10.1186/s40364-025-00861-4

Biomarker Research

CORRESPONDENCE Open Access

The lung cancer-associated blood biomarker hPG_{80} exhibits a reversible increase in response to smoking in asymptomatic individuals

Bérengère Vire[1*], Léa Payen[2,3,4], Claire Vignault[5], Véronique Hofman[6], Charles Hugo Marquette[7], Jean-Philippe Berthet[8], Jacques Boutros[7], Marius Ilie[6], Guillaume Penaranda[9], Philippe Pourquier[1], Nassima Mimoun[1], Dominique Joubert[1], Alexandre Prieur[1] and Paul Hofman[6,10*]

Abstract

The blood biomarker hPG_{80} is linked to multiple solid tumors, including lung cancer. This study examined blood hPG_{80} levels of asymptomatic individuals and patients with non-small cell lung cancer (NSCLC), categorized by their smoking and chronic obstructive pulmonary disease (COPD) status. Plasma hPG_{80} levels were measured across five cohorts of patients, including 396 NSCLC patients, 200 NSCLC cancer-free COPD patients, 369 asymptomatic never smokers, 278 asymptomatic current smokers, and 235 asymptomatic former smokers. Receiver operating characteristic (ROC) curves assessed diagnostic accuracy. In asymptomatic current smokers, hPG_{80} levels were significantly higher (6.70 pM (IQR: 5.13–11.29)) than those in gender- and age-matched never smokers (2.50 pM (IQR: 1.70–3.70; $p < 0.0001$). In contrast, gender- and age-matched former smokers showed a return to normal hPG_{80} levels (2.29 pM (IQR: 1.61–2.97)). In multivariate analysis, age and smoking status were significantly associated with elevated levels of hPG_{80} (*p*-values of 0.0319 and < 0.0001, respectively). Levels of hPG_{80} in current smokers were not different from levels found in age-matched patients with NSCLC or COPD (6.60 pM (IQR: 4.36–11.22) and 6.07 pM (IQR: 3.99–11.69), respectively). In NSCLC and COPD patients, hPG_{80} levels were independent of the smoking status. When comparing asymptomatic and NSCLC-diagnosed former smokers, the AUC was 0.85 (95% CI:0.80–0.90, $p < 0.0001$). The AUC was equal to 0.53 (95% CI: 0.45–0.60, $p = 0.4436$) for current smokers. Our findings identify hPG_{80} as both a reversible marker of active smoking and a diagnostic biomarker of NSCLC. This dual role supports its potential use in risk stratification and early detection, particularly among non-COPD former smokers.

*Correspondence:
Bérengère Vire
b.vire@biodena.care
Paul Hofman
HOFMAN.P@chu-nice.fr

Full list of author information is available at the end of the article

© The Author(s) 2025. **Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by/4.0/. The Creative Commons Public Domain Dedication waiver (http://creativecommons.org/publicdomain/zero/1.0/) applies to the data made available in this article, unless otherwise stated in a credit line to the data.

To the Editor

Lung cancer is the leading cause of cancer death (GLOBOCAN 2022) [1], with smoking as the main risk factor for NSCLC [2]. While Low-Dose Computed Tomography (LD-CT) improves early detection, it lacks specificity [3]. Blood biomarkers like CEA, CYFRA21-1, and SCC-Ag are less invasive but have limited sensitivity for early-stage NSCLC detection [4].

hPG_{80} (circulating progastrin) is a promising blood biomarker for detection of solid tumors [5]. Activation of oncogenic pathways (APC/β-catenin, Ras) drives secretion of hPG_{80} in cancer cells, where it promotes tumorigenic processes including cancer stem cell survival [6]. Previous work has shown elevated hPG_{80} in NSCLC [5, 7] but it remains unknown whether tobacco exposure can influence hPG_{80} and whether such changes are reversible. hPG_{80} levels were also measured in patients with COPD, a common smoking-related condition not considered a confounding factor of tobacco consumption [8].

Plasma hPG_{80} was measured in five cohorts: treatment-naïve NSCLC patients ($n = 396$), COPD patients without NSCLC ($n = 200$), and asymptomatic never ($n = 369$), current ($n = 278$), and former smokers ($n = 235$) (Table S1 and Supplementary methods). Quantification was performed using the DxPG80.lab ELISA [9], with gender- and age-matched comparisons. Multivariate analysis was performed to assess the effects of gender, age, pack-years, and smoking history on hPG_{80} variations (Supplementary methods).

Smoking induces an increase in hPG_{80} blood levels in asymptomatic individuals

Active smoking was strongly associated with elevated hPG_{80} in asymptomatic individuals: median 6.70 pM (IQR: 5.13–11.29) versus 2.50 pM (IQR: 1.70–3.70) in gender- and age-matched never smokers ($p < 0.0001$). Levels correlated to smoking duration and cumulative exposure (Fig. 1A–C and Table S2). In multivariate analysis, smoking status and age were independently associated with higher circulating hPG_{80} levels (Table S3 and Fig. S1). Strikingly, former smokers without NSCLC had hPG_{80} levels similar to never smokers (median 2.29 pM (IQR: 1.61–2.97)) (Fig. 1Aand Table S2). Notably, 82% of former smokers had hPG_{80} levels below the limit of quantification (LoQ). hPG_{80} levels drop within the first year after quitting smoking (low in 88% of recent quitters), suggesting that the elevation in smokers is reversible (Fig. S2). The effect size (4.41; 95% CI: 3.94–5.45; $p < 0.0001$) further supports the robustness of these findings (Table S4A).

hPG_{80} levels in NSCLC and COPD patients

In NSCLC patients, hPG_{80} was significantly higher than in age-matched asymptomatic never smokers (6.11 pM (IQR: 4.11–11.22) versus 3.20 pM (IQR: 2.20–4.80); $p < 0.0001$) (Fig. 1D), regardless of the stage or histology (Fig. S3), and independent of the smoking status (Fig. 1E). COPD patients without NSCLC also displayed elevated hPG_{80} (6.35 pM (IQR: 4.10–13.31) versus 3.30 pM (IQR: 2.40–5.05) in age-matched asymptomatic never smokers; $p < 0.0001$) (Table S2 and Fig. 1F). The hPG_{80} increase in COPD patients was independent of disease severity, smoking status, or the presence of NSCLC (Fig. 1F–H).

hPG_{80} levels in NSCLC compared to their respective self-declared cancer free age-matched controls

When NSCLC patients were compared to their respective controls matched for smoking status, the levels of hPG_{80} were significantly higher in never and former smokers, but not different from current smokers (Fig. 2A–C and Table S2). Effect size analysis confirms a clear median difference between NSCLC patients and former smokers (4.44; 95% CI: 3.38–5.36; $p < 0.0001$) (Table S4B). Diagnostic performance (AUC) was highest in former smokers (0.85 (95% CI = 0.80–0.90), $p < 0.0001$) and never smokers (0.70 (95% CI = 0.59–0.82), $p = 0.0022$), but negligible in current smokers (0.53 (95% CI = 0.45–0.60), $p = 0.4436$) (Fig. 2D–F). For former smokers, ROC analysis identified an optimal cutoff of 4 pM (Youden's index), with 81% sensitivity and 80% specificity.

Discussion

This study shows a strong link between hPG_{80} blood levels and smoking, suggesting its potential use as: i) a motivational tool for quitting (due to post-cessation decline), ii) a risk marker in former smokers without COPD (Fig. 2G); and iii) a broad cancer detection biomarker in high-risk groups, given smoking's link to multiple tumor types.

Nicotine can activate the Wnt/β-catenin pathway in bronchial epithelial cells [10]. This may trigger hPG_{80} secretion *via* the Wnt/β-catenin pathway, which directly targets its gene promoter. Chronic smoking-related inflammation and pre-neoplastic changes could further drive hPG_{80} expression before cancer appears. Given hPG_{80}'s role in cancer stem cell survival [11], its elevation may promote field carcinogenesis and contribute to the higher cancer risk in smokers.

This study holds some limitations, including the limited associated clinical data for asymptomatic individuals and the incomplete smoking history of COPD patients. In addition, no comparison with other biomarkers was performed.

In conclusion, our findings support a dual role for hPG_{80}: as a biomarker of smoking-related biological risk and as a diagnostic biomarker for lung cancer. Therefore, hPG_{80} could become a valuable tool for early NSCLC detection in non-COPD former smokers, who represent

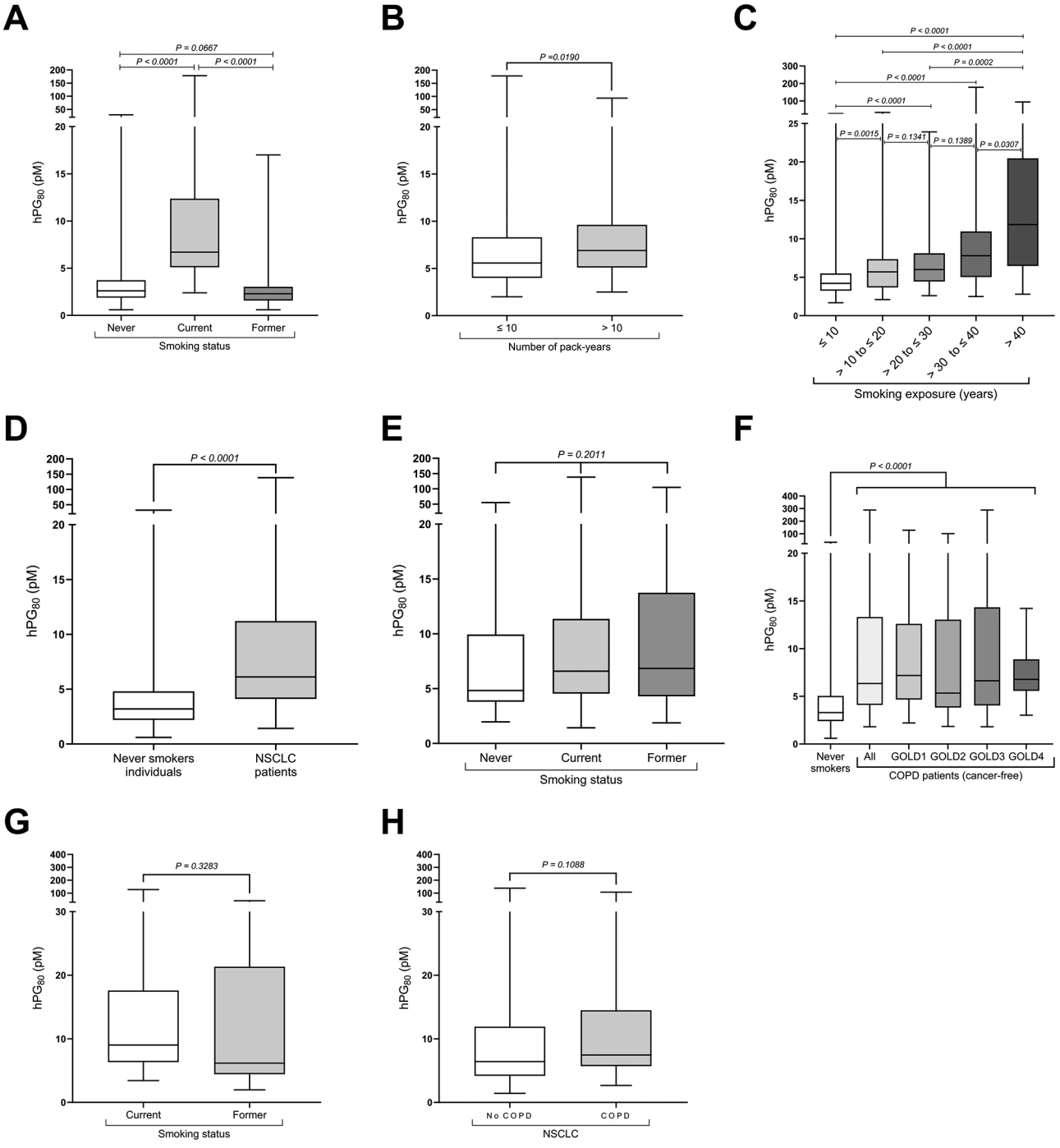

Fig. 1 Impact of smoking, NSCLC and COPD on hPG_{80} levels. **A**. Comparison between gender- and age-matched current smokers, never smokers and former smokers ($n = 110$). **B**. hPG_{80} levels in current smokers ($n = 83$) stratified according to the number of pack-years (≤10 and > 10). **C**. Incidence of the number of years of smoking exposure on hPG_{80} levels in current smokers. **D**. Comparison of hPG_{80} levels between age-matched never smokers and NSCLC patients ($n = 289$). **E**. hPG_{80} levels stratified according to the smoking status: never ($n = 40$), current ($n = 224$) and former ($n = 127$). **F**. Comparison of age-matched never smokers and COPD patients ($n = 145$), stratified according to the gold status (GOLD1, $n = 40$; GOLD2, $n = 60$; GOLD3, $n = 39$; and GOLD4, $n = 6$) or pooled (all stages). **G**. hPG_{80} levels in cancer-free COPD patients according to the smoking status: current ($n = 27$) and former ($n = 18$). **H**. hPG_{80} levels in NSCLC patients stratified according to the COPD status: no COPD ($n = 364$) and COPD ($n = 32$). Boxes represent the interquartile range, and the horizontal line across each box indicates median values. The statistical differences were evaluated using the Kruskall-Wallis test and the Mann-Whitney *U* test

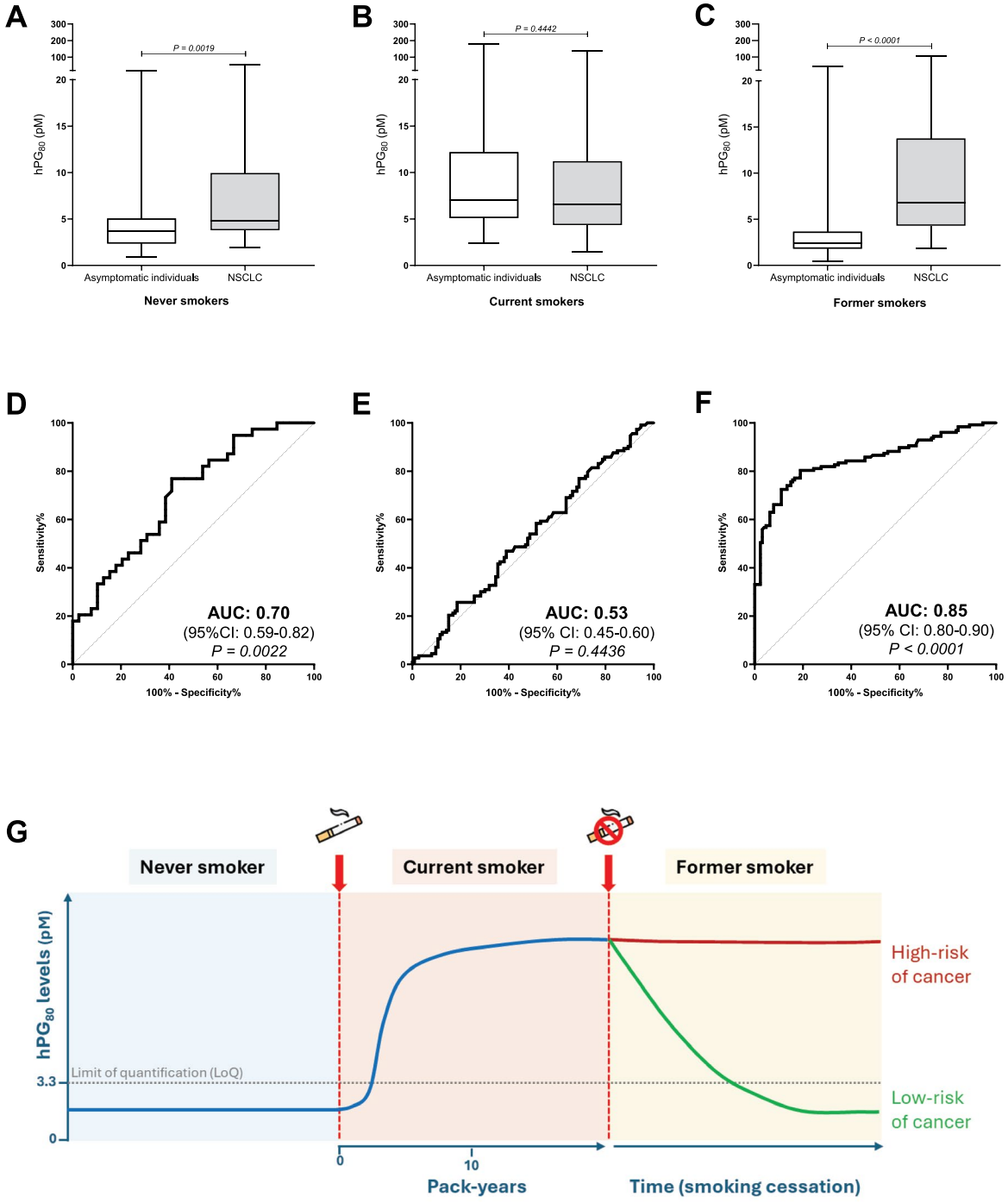

Fig. 2 hPG_{80} in former smokers: strong diagnostic value and potential marker of residual cancer risk. Comparison of hPG_{80} levels in NSCLC patients versus their respective age-matched controls, stratified according to the smoking status: **A**. never ($n = 39$), **B**. current ($n = 113$) and **C**. former smokers ($n = 127$). Boxes represent the interquartile range, and the horizontal line across each box indicates median values. The statistical differences were evaluated with the Mann-Whitney *U* test. ROC curve analyses corresponding to each comparison: **D**. never, **E**. current and **F**. former smokers. AUC: area under the curve. **G**. Hypothetical link between the hPG_{80} levels and risk of cancer in former smokers. hPG_{80} levels are low in never smokers, rise with smoking exposure up to 10 pack-years, and may decrease after cessation in some individuals, while persistently elevated levels could indicate a higher risk of cancer

18% of the adult population [12], warranting prospective validation in screening programs.

Abbreviations

AUC	Area under the curve
95% CI	95% Confidence interval
COPD	Chronic obstructive pulmonary disease
IQR	Interquartile range
LD-CT	Low-dose computed tomography
LoQ	Limit of quantification
NSCLC	Non-small cell lung cancer
ROC	Receiver operating characteristic

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s40364-025-00861-4.

Supplementary Material 1

Acknowledgements
The authors would like to thank the staff members of the Laboratory of Clinical and Experimental Pathology, Centre Hospitalier Universitaire de Nice, France, for assistance in sample retrieval from the BB-0033-00025 biobank. We would also like to thank all the staff members of Progastrin Manufacturing and Biogroup. This work was supported by the French National Research Agency ("IHU RespirERA" France 2030 program # ANR-23-IAHU-007).

Author contributions
BV, DJ and AP: Conceptualization, Methodology, Investigation, Visualization, Writing -original draft, Writing – review & editing. LP, CV, VH, CHM, JPB, JB, MI, PP and NM: Writing – review & editing. GP: Formal analysis, Writing – review & editing. PH: Conceptualization, Writing -original draft, Writing – review & editing. All authors read and approved the final manuscript.

Funding
Progastrin Manufacturing funded the study.

Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
DJ, AP, NM, PP and BV are employed by Progastrin Manufacturing. All the other coauthors declare no competing interests.

Author details
[1]Progastrin Manufacturing, Grabels, France
[2]Institute of Pharmaceutical and Biological Sciences (ISPB), Claude Bernard Lyon I, Lyon, France
[3]Department of Biochemistry and Molecular Biology, Lyon-Sud Hospital, Hospices Civils de Lyon, Pierre-Bénite, France
[4]Center for Innovation in Cancerology of Lyon (CICLY) EA 3738, Faculty of Medicine and Maieutic Lyon Sud, Claude Bernard University Lyon I, Oullins, France
[5]Service Recherche Clinique Et Innovation, Laboratoire Biogroup, Besançon, France
[6]IHU respirERA, Laboratoire de Pathologie Clinique Et Expérimentale, Centre Hospitalo-Universitaire de Nice (CHUN), FHU oncoage, IRCAN Inserm U1081, BB-0033-00025, Université Côte d'Azur, Nice, France
[7]IHU respirERA, Service de Pneumologie Et d'Oncologie Thoracique, Centre Hospitalo-Universitaire de Nice (CHUN), FHU oncoage, Université Côte d'Azur, Nice, France
[8]IHU respirERA, Service de Chirurgie Thoracique, Centre Hospitalo-Universitaire de Nice (CHUN), FHU oncoage, Université Côte d'Azur, Nice, France
[9]Biogroup Provence, Marseille, France
[10]European Liquid Biopsy Society, Martinistrasse, Hamburg, Germany

Received: 19 August 2025 / Accepted: 17 October 2025
Published online: 13 November 2025

References

1. Ji Y, Zhang Y, Liu S, Li J, Jin Q, Wu J, et al. The epidemiological landscape of lung cancer: current status, temporal trend and future projections based on the latest estimates from Globocan 2022. J Natl Cancer Cent. 2025;5:278–86.
2. Mazzilli SA, Rahal Z, Rouhani MJ, Janes SM, Kadara H, Dubinett SM, et al. Translating premalignant biology to accelerate non-small-cell lung cancer interception. Nat Rev Cancer. 2025;1–14.
3. Oudkerk M, Liu S, Heuvelmans MA, Walter JE, Field JK. Lung cancer LDCT screening and mortality reduction - evidence, pitfalls and future perspectives. Nat Rev Clin Oncol. 2021;18:135–51.
4. Okamura K, Takayama K, Izumi M, Harada T, Furuyama K, Nakanishi Y. Diagnostic value of CEA and CYFRA 21–1 tumor markers in primary lung cancer. Lung cancer. 2013;80:45–9.
5. You B, Mercier F, Assenat E, Langlois-Jacques C, Glehen O, Soulé J, et al. The oncogenic and druggable hPG80 (progastrin) is overexpressed in multiple cancers and detected in the blood of patients. EBioMedicine. 2019;1–12.
6. Giraud J, Foroutan M, Boubaker-Vitre J, Grillet F, Homayed Z, Jadhav U, et al. Progastrin production transitions from Bmi1+/Prox1+ to Lgr5high cells during early intestinal tumorigenesis. Transl Oncol. 2021;14:101001.
7. You B, Couraud S, Ceruse P, Badet L, Paparel P, Durand A, et al. Diagnostic value of the wnt target and cancer-associated blood biomarker hPG80: ONCOPRO case-control prospective study. Biomark Res. 2025;13:91.
8. Young RP, Hopkins RJ, Christmas T, Black PN, Metcalf P, Gamble GD. COPD prevalence is increased in lung cancer, independent of age, sex and smoking history. Eur Respir J. 2009;34:380–86.
9. Cappellini M, Flaceliere M, Saywell V, Soule J, Blanc E, Belouin F, et al. A novel method to detect hPG80 (human circulating progastrin) in the blood. Anal Methods-Uk. 2021;13:4468–77.
10. Wang C, Xu X, Jin H, Liu G. Nicotine may promote tongue squamous cell carcinoma progression by activating the Wnt/β-catenin and Wnt/PCP signaling pathways. Oncol Lett. 2017;13:3479–86
11. Prieur A, Cappellini M, Habif G, Lefranc M-P, Mazard T, Morency E, et al. Targeting the wnt pathway and cancer stem cells with anti-progastrin humanized antibodies as a potential treatment for K-RAS-Mutated colorectal cancer. Clin Cancer Res [Internet]. 2017;1–15. Available from: http://clincancerres.aacrjournals.org/2460708d-e0df-49d6-8299-995e5e10b752,.
12. Guignard R, Gaudebout A, Andler R, Pasquereau A, Beck F, Nguyen-Thanh V. Smoking cessation in mainland France: recent trends and associated factors based on the santé publique France health barometer 2021. Santé Publique Fr. 2025.

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.