Title

Concerns Regarding the Utility of High-Risk Pancreatic Cancer Surveillance

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Authors

Dasaro, Christopher

Prasad, Vinay

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could result in varying levels of carcinogenic substances, like nicotine. We believe that a more rigorous quantification method for tobacco consumption and its effects is necessary. Further confirmation of whether there is an interaction between the 2 forms of tobacco consumption would provide a better understanding of the association of tobacco with cancer mortality risk.

Second, other covariates could be more finely divided, such as splitting body mass index to further differentiate obesity. Alcohol intake could be categorized by types of alcohol and daily intake amounts. Family history could be specified to identify high-risk hereditary cancers, like Peutz-Jeghers syndrome or Lynch syndrome. Conducting subgroup analyses on these populations would provide a better understanding of tobacco's effect on different populations. Furthermore, we were worried about the possible confounding by indication due to the policy of cancer screening targeting high-risk smoking populations. We hope for an explanation of the related policies. In conclusion, further research is needed to quantify and convert the 2 main types of tobacco and study their associations with different populations to fill the knowledge gaps in this area.

Ping-Hao Chiang
Chieh-Hsuan Tsai, MD

Author Affiliations: Chiayi Chang Gung Memorial Hospital, Puzi City, Chiayi, Taiwan (Chiang); Ditmanson Medical Foundation Chia-Yi Christian Hospital, Chiayi City, Taiwan (Tsai).

Corresponding Author: Chieh-Hsuan Tsai, MD, Ditmanson Medical Foundation Chia-Yi Christian Hospital, No. 539 Zhongxiao Rd, East District, Chiayi City 600, Taiwan (aurora90083@gmail.com).

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Conflict of Interest Disclosures: None reported.

1. Le NT, Phan CV, Pham YT, et al. Waterpipe tobacco smoking and risk of cancer mortality. *JAMA Oncol*. 2024;10(9):1237-1244. doi:10.1001/jamaoncol.2024.1939

In Reply We thank Chiang and Tsai for the interest and thoughtful comments regarding our article.[1] The authors pointed out that the use of sessions per day to calculate tobacco consumption might introduce statistical inaccuracies, with which, to some extent, we agree. While smoking pack-years has been used extensively in smoking-related studies for lung cancer and other chronic diseases, it has also been recognized that it is the number of years of smoking (or duration of smoking) that plays an important role and measurement in the evaluation of the association of smoking with health outcomes, rather than the intensity or how much tobacco an individual consumes per day.[2] In that sense, the intensity and duration of smoking should be used in smoking-related studies and clinical practice. We also agree that different forms of tobacco consumption might result in different levels of carcinogenic substances, including tobacco-specific nitrosamine and polycyclic aromatic hydrocarbons, and a more precise quantification for tobacco consumption is warranted. In an additional analysis, we found that alcohol consumption interacts with cigarette smoking and waterpipe smoking in their association with cancer mortality (P for interaction < .001).

We also agree that a subgroup analysis would provide additional insights into the effect of smoking in different population. However, information on family history of cancer, Peutz-Jeghers syndrome, or Lynch syndrome is unavailable, which prohibited us from conducting a subgroup analysis. Finally, we appreciate the authors for raising the issue of potential confounding by indication due to a policy of cancer screening targeting high-risk smoking populations. A recent study that used National Health Interview Survey data to assess patterns of cancer screening among never, former, and current adult smokers in the US from 2010 to 2015 found that a high-risk population receives suboptimal cancer screening, which might be beneficial from measures to promote screening and meet Healthy People 2020 targets.[3] Therefore, similar efforts, including those of policy and interventions in Vietnam and other low-resource settings, are warranted to (1) identify barriers to cancer screening among people who smoke and (2) support relevant screening modalities among this population.

Ngoan Tran Le, MD, PhD
Jian-Min Yuan, MD, PhD
Hung N. Luu, MD, PhD

Author Affiliations: Institute of Research and Development, Duy Tan University, Da Nang City, Vietnam (Le); Department of Occupational Health, Institute for Preventive Medicine and Public Health, Hanoi Medical University, Ha Noi City, Vietnam (Le); University of Pittsburgh Medical Center Hillman Cancer Center, Pittsburgh, Pennsylvania (Yuan, Luu); Department of Epidemiology, School of Public Health, University of Pittsburgh, Pittsburgh, Pennsylvania (Yuan, Luu).

Corresponding Authors: Ngoan Tran Le, MD, PhD, Department of Occupational Health, Hanoi Medical University, 1 Ton That Tung, Hanoi 116177, Vietnam (letngoan@hmu.edu.vn); Hung N. Luu, MD, PhD, UPMC Hillman Cancer Center, University of Pittsburgh Medical Center, 5150 Centre Ave, Ste 4C, Pittsburgh, PA 15232 (hnl11@pitt.edu).

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2. Pleasants RA, Rivera MP, Tilley SL, Bhatt SP. Both duration and pack-years of tobacco smoking should be used for clinical practice and research. *Ann Am Thorac Soc*. 2020;17(7):804-806. doi:10.1513/AnnalsATS.202002-133VP

3. Sanford NN, Sher DJ, Butler S, et al. Cancer screening patterns among current, former, and never smokers in the United States, 2010-2015. *JAMA Netw Open*. 2019;2(5):e193759. doi:10.1001/jamanetworkopen.2019.3759

Concerns Regarding the Utility of High-Risk Pancreatic Cancer Surveillance

To the Editor Blackford et al[1] report outcomes for 26 of 1731 individuals who were diagnosed with pancreatic ductal adenocarcinoma (PDAC) in their high-risk screening clinic. To assess the benefits and harms of the approach, outcomes for the 1705 patients who did not have PDAC detected must be reported. How many had a suspicious screening result? How many underwent follow-up imaging? How many biopsies or surgeries were performed revealing benign or non-PDAC findings? How many complications/deaths occurred among these patients from downstream sequelae?

Importantly, just 26 of 1731 patients (1.5%) were diagnosed with pancreatic cancer. Can the authors provide the

incidence with person-time as the denominator? This allows for comparison against baseline population lifetime risk, which is 1.7%,[2] to see just how high-risk patients in this clinic were.

Furthermore, 26% of diagnosed individuals were found to have metastatic disease at diagnosis. It is hard to imagine these patients benefit from the program because the disease was already incurable. This fact raises the question if the disease is nearly micrometastatic even at early presentation, and whether screening is misguided.

Finally, comparing survival times among the 26 patients against Surveillance, Epidemiology, and End Results is misguided for 2 reasons. One, lead time is likely larger than even the sensitivity analysis, and is entirely unknown. The types of people who participate in the clinic are fundamentally unique. Can the authors provide the median household income? Also, can they report insurance status for clinic patients?

Christopher Dasaro, BS
Vinay Prasad, MD, MPH

Author Affiliations: Lewis Katz School of Medicine at Temple University, Philadelphia, Pennsylvania (Dasaro); Department of Epidemiology and Biostatistics, University of California, San Francisco (Prasad).

Corresponding Author: Christopher Dasaro, BS, Lewis Katz School of Medicine at Temple University, 3500 N Broad St, Philadelphia, PA 19140 (dasarochristopher@gmail.com).

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1. Blackford AL, Canto MI, Dbouk M, et al. Pancreatic cancer surveillance and survival of high-risk individuals. *JAMA Oncol*. 2024;10(8):1087-1096. Published online July 3, 2024. doi:10.1001/jamaoncol.2024.1930

2. Cancer of the Pancreas - Cancer Stat Facts. SEER. Accessed July 12, 2024. https://seer.cancer.gov/statfacts/html/pancreas.html

In Reply In our recent study,[1] we compared the survival of patients who developed pancreatic cancer under pancreas surveillance to that of a matched US cohort. Many of the questions asked by Dasaro and Prasad we address in previous publications,[2,3] cited in the article, including imaging findings and surgical pathologic findings, and an estimate of the overall risk of pancreatic cancer in the cohort (1 per 194 patient-years). We have also reported on outcomes of surgical treatment of suspicious pancreatic lesions.[4] Very few pancreatic imaging abnormalities raise concern or need biopsy or surgical resection.

Estimating the relative risk of pancreatic ductal adenocarcinoma was not an end point of our study,[1] but we now provide this analysis. Our cohort of 1731 patients included 106 106 person-years of follow-up, corresponding to a pancreatic cancer incidence rate of 26 / 106 106 = 0.00025, or 25 cases per 100 000 person-years. To calculate the incidence in a general population cohort of the same age, sex, and race and ethnicity, we analyzed the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) data (SeerStat; version 8.4.3). Age-adjusted incidence rates were determined separately for men and women according to race and ethnicity (Hispanic, non-Hispanic Asian/Pacific Islander, non-Hispanic Black, non-Hispanic White) by age in 5-year intervals (ie, 25-29 years, 30-34 years) from 2000 to 2021, matching the Cancer of the Pancreas Screening (CAPS) cohort surveillance period and leveraging all 22 SEER registries (representing approximately 50% of the US population). Using each CAPS participant's sex, race and ethnicity, and age at last screening, we computed the number of pancreatic cancers expected in a SEER cohort. The observed-to-expected (OE) ratio was calculated and 95% CIs were estimated using a bootstrap approach with 10 000 simulations. We calculated a cohort matching SEER would have had an incidence of 6.5 pancreatic cancer cases over their observed lifetime; compared with our CAPS cohort, the OE ratio is 26 / 6.5 = 4.0; 95% CI, 2.6-5.6; $P < .001$. This 4-fold elevated risk in our CAPS cohort corresponds to a lifetime risk of 4 × 1 / 58 (the current estimated lifetime risk per the American Cancer Society) = 7%, which matches other estimates. Pancreatic surveillance criteria[5,6] aim to enroll participants with 5% or higher estimated lifetime pancreatic cancer risk; many of our patients have an estimated lifetime risk of 10% or higher.

Regarding the comment about metastatic disease, 6 of the 7 patients who presented with stage IV disease had discontinued surveillance, which highlights the benefits of surveillance because most patients diagnosed with pancreatic cancer outside of surveillance present with stage IV disease. Though we need to better understand barriers and other factors that can lead some patients to drop surveillance, the characteristics of the patients who discontinued surveillance were similar in many respects to those who maintain surveillance. We agree that patients who undergo screening/surveillance may have certain differences from the general population with respect to general health and health service-seeking behavior.

We observed a much lower disease-specific mortality in our cohort that was closely related to the significant downstaging of the disease with regular surveillance, which is especially important for a cancer where there is often very rapid death. Our results are an important step forward in the fight against a very lethal disease.

Amanda L. Blackford, ScM
Marcia Irene Canto, MD, MHS
Michael Goggins, MBBCh, MD

Author Affiliations: Johns Hopkins University School of Medicine, Baltimore, Maryland.

Corresponding Author: Marcia Irene Canto, MD, MHS, Johns Hopkins University School of Medicine, 1800 Orleans St, Blalock 407, Baltimore, MD 21287 (mcanto1@jhmi.edu).

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1. Blackford AL, Canto MI, Dbouk M, et al. Pancreatic cancer surveillance and survival of high-risk individuals. *JAMA Oncol*. 2024;10(8):1087-1096. doi:10.1001/jamaoncol.2024.1930

2. Dbouk M, Katona BW, Brand RE, et al. The multicenter cancer of pancreas screening study: impact on stage and survival. *J Clin Oncol*. 2022;40(28):3257-3266. doi:10.1200/JCO.22.00298

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4. Canto MI, Kerdsirichairat T, Yeo CJ, et al. Surgical outcomes after pancreatic resection of screening-detected lesions in individuals at high risk for developing pancreatic cancer. *J Gastrointest Surg*. 2020;24(5):1101-1110. doi:10.1007/s11605-019-04230-z

5. Canto MI, Harinck F, Hruban RH, et al; International Cancer of the Pancreas Screening (CAPS) consortium. International Cancer of the Pancreas Screening (CAPS) Consortium summit on the management of patients with increased risk for familial pancreatic cancer. *Gut*. 2013;62(3):339-347. doi:10.1136/gutjnl-2012-303108

6. Goggins M, Overbeek KA, Brand R, et al; International Cancer of the Pancreas Screening (CAPS) consortium. Management of patients with increased risk for familial pancreatic cancer: updated recommendations from the International Cancer of the Pancreas Screening (CAPS) Consortium. *Gut*. 2020;69(1):7-17"https://pubmed.ncbi.nlm.nih.gov/31672839". doi:10.1136/gutjnl-2019-319352

CORRECTION

Change of Article Status to Open Access: The Original Investigation titled "Systemic Anticancer Therapy and Overall Survival in Patients With Very Advanced Solid Tumors,"[1] published online May 16, 2024, and in the July 2024 issue of *JAMA Oncology*, has changed license status to open access (CC-BY-NC-ND license). This article was updated online.

1. Canavan ME, Wang X, Ascha MS, et al. Systemic anticancer therapy and overall survival in patients with very advanced solid tumors. *JAMA Oncol*. 2024;10(7):887-895. doi:10.1001/jamaoncol.2024.1129

Errors in Figures 2 and 3: In the Original Investigation titled "First-Line Systemic Treatment for Initially Unresectable Colorectal Liver Metastases: Post Hoc Analysis of the CAIRO5 Randomized Clinical Trial,"[1] published online November 21, 2024, and in the January 2025 issue, there were errors in Figures 2 and 3. In Figure 2, the label for panel A should be "Right-sided and/or RAS or *BRAF*^{V600E}-mutated primary tumors," and the label for panel B should be "Left-sided and RAS and *BRAF*^{V600E} wild-type primary tumors." The portion of the figure legend marked "'FOLFIRI + bevacizumab" should be "'FOLFOXIRI + bevacizumab," and the portion of the figure caption marked "FOLFOX plus irinotecan and bevacizumab" should be "'FOLFOX plus irinotecan (FOLFOXIRI) and bevacizumab." In Figure 3, the blue line in the figure legend should be labeled "Incomplete local treatment," and the red line "No local treatment." This article was corrected online.

1. Bond MJG, Bolhuis K, Loosveld O, et al. First-line systemic treatment for initially unresectable colorectal liver metastases: post hoc analysis of the CAIRO5 randomized clinical trial. *JAMA Oncol*. Published online November 21, 2024. doi:10.1001/jamaoncol.2024.5174