Received: 11 April 2022 | Revised: 14 June 2022 | Accepted: 17 August 2022

DOI: 10.1002/cac2.12357

CANCER COMMUNICATIONS Open Access

LETTER TO THE EDITOR

Smoking, smoking cessation, and survival after cancer diagnosis in 128,423 patients across cancer types

Dear Editor,

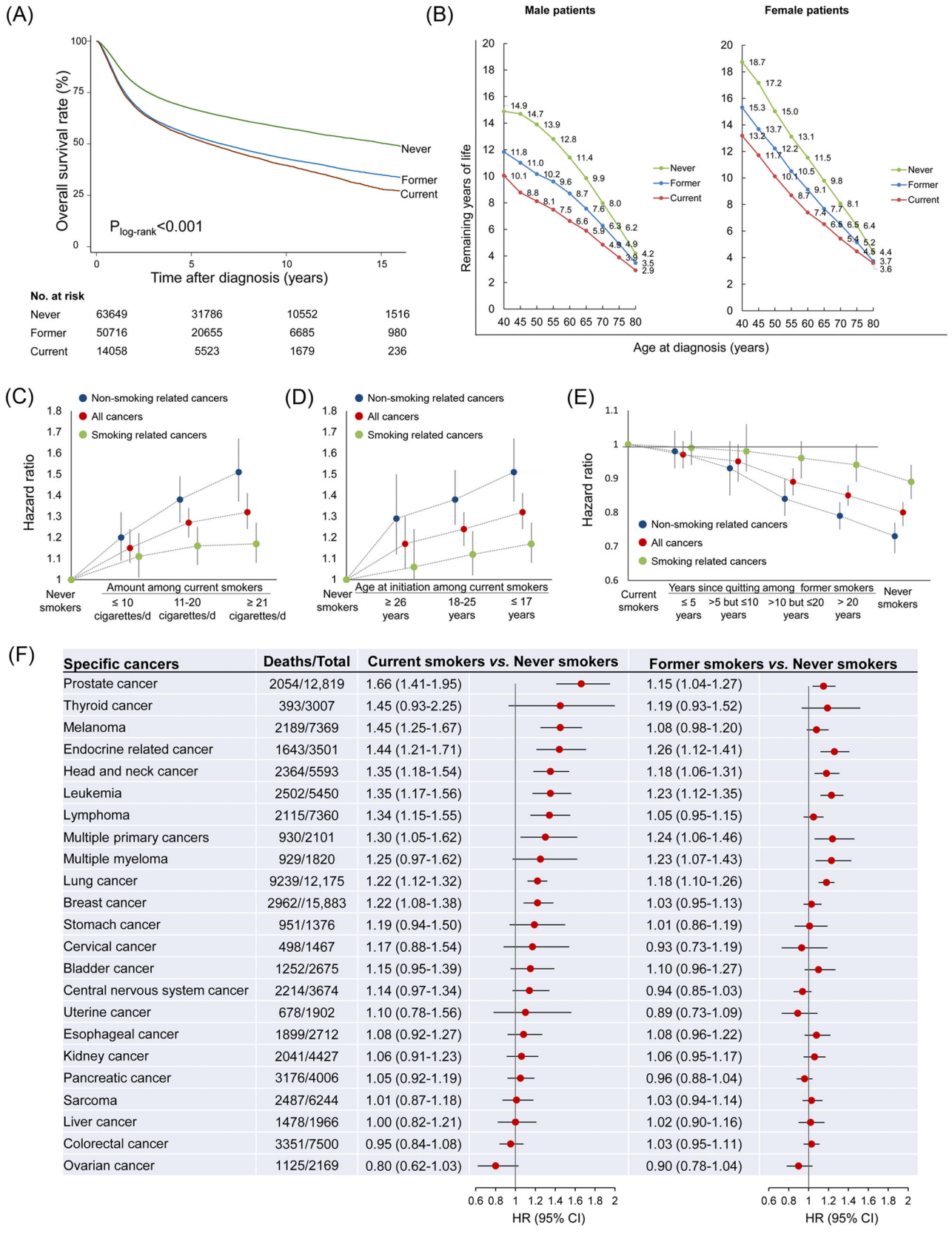
Given the systemic and substantial health consequences of smoking and the significant cancer risk from smoking [1, 2], it is expected that cancer patients would quit smoking after cancer diagnosis. However, the smoking rate among cancer survivors is only slightly lower than that among the general population [3, 4], and 64% of smokers diagnosed with cancer continued to smoke even after they learned they had cancer [5]. In addition, some former smokers may resume smoking after surviving cancer [6]. A number of previous studies have investigated the association between smoking and clinical outcomes in cancer patients [1, 7–10]. Nevertheless, most studies were conducted in smoking-related cancers, and evidence for non-smoking-related cancers is limited. There is an urgent need for more convincing evidence showing the harms of smoking and the benefits of smoking cessation to promote smoking cessation in cancer patients and survivors. We systematically studied the associations of smoking status, smoking intensity, age at initiation, and smoking cessation at cancer diagnosis with all-cause mortality in a prospective cohort of 128,423 cancer patients across 23 cancer types from the MD Anderson Cancer Patients and Survivors Cohort.

Among the 128,423 cancer patients enrolled, 14,058 (10.9%) were current smokers, 50,716 (39.5%) were former smokers, and 63,649 (49.6%) were never smokers at diagnosis. Supplementary Table S1 shows the selected patient characteristics at cohort entry by smoking status. Supplementary Figure S1 shows the percentage of never, former, and current smokers across 23 cancer types. During a median follow-up period of 7.6 years (range, 0-19.1 years), 646,063 person-years were accumulated, and 53,817 (41.9%) deaths were recorded. Patients who never smoked had the best survival, while patients who were currently smoking had the worst survival (Figure 1A). Compared to never smoking, after multivariable adjustment, the HRs were 1.09 (95% CI = 1.06-1.11) for former smoking and 1.19 (95% CI = 1.16-1.23) for current smoking). Compared with never smokers, former smokers had up to 3.7 years shortened life expectancy and current smokers had up to 5.9 years shortened life expectancy (Figure 1B).

As shown in Figure 1C, compared with never smokers, the risk of death increased as the number of cigarettes smoked per day increased among current smokers, and the HR was 1.15 (95% CI = 1.08-1.24), 1.27 (95% CI = 1.20-1.34), or 1.32 (95% CI = 1.24-1.41) for those who smoked ≤10, 11-20, or ≥21 cigarettes/day, respectively. We also analyzed smoking consumption as a continuous variable, and consistent results were observed (Supplementary Figure S2). Similarly, there was a dose-response relationship between younger age at smoking initiation and the risk of death (Figure 1D), and the HR was 1.17 (95% CI = 1.05-1.30), 1.24 (95% CI = 1.16-1.32), or 1.32 (95% CI = 1.24-1.41) for those who started smoking at the age of ≥26, 18-25, or ≤17 years old, respectively. We also assessed the association between pack-years with all-cause mortality, and we observed consistent results (Supplementary Figure S3). As shown in Figure 1E, compared with current smokers, longer time since quitting among former smokers was associated with greater reduction in the risk of death from all cancers, with a reduction of 3% (HR = 0.97, 95% CI = 0.93-1.01), 5% (HR = 0.95, 95% CI = 0.89-1.00), 11% (HR = 0.89, 95% CI = 0.85-0.93), and 15% (HR = 0.85, 95% CI = 0.82-0.88) for quitting ≤5, >5 but ≤10, >10 but ≤20, or >20 years ago, respectively. In contrast, the reduction in the risk of death was greatest for never smokers, by 20% (HR = 0.80, 95% CI = 0.76-0.83) relative to smokers. The harms of cigarette smoking and the benefits of smoking cessation, were stronger among patients with non-smoking-related cancers than among patients with smoking-related cancers (Figures 1C-E).

Compared with never smoking, current smoking was associated with an increased risk of death for 20 of 23 (statistically significant in 9 of 23) cancer types (Figure 1F). Similarly, former smokers had an increased risk for 18 of the 23 (statistically significant in 7 of 23) cancer types, but the risk was generally smaller than that for current smokers (Figure 1F). As shown in Supplementary Figure S4, the

Abbreviations: HR, hazard ratio; CI, confidence interval.



Specific cancers	Deaths/Total	Current smokers *vs.* Never smokers	Former smokers *vs.* Never smokers
Prostate cancer	2054/12,819	1.66 (1.41-1.95)	1.15 (1.04-1.27)
Thyroid cancer	393/3007	1.45 (0.93-2.25)	1.19 (0.93-1.52)
Melanoma	2189/7369	1.45 (1.25-1.67)	1.08 (0.98-1.20)
Endocrine related cancer	1643/3501	1.44 (1.21-1.71)	1.26 (1.12-1.41)
Head and neck cancer	2364/5593	1.35 (1.18-1.54)	1.18 (1.06-1.31)
Leukemia	2502/5450	1.35 (1.17-1.56)	1.23 (1.12-1.35)
Lymphoma	2115/7360	1.34 (1.15-1.55)	1.05 (0.95-1.15)
Multiple primary cancers	930/2101	1.30 (1.05-1.62)	1.24 (1.06-1.46)
Multiple myeloma	929/1820	1.25 (0.97-1.62)	1.23 (1.07-1.43)
Lung cancer	9239/12,175	1.22 (1.12-1.32)	1.18 (1.10-1.26)
Breast cancer	2962//15,883	1.22 (1.08-1.38)	1.03 (0.95-1.13)
Stomach cancer	951/1376	1.19 (0.94-1.50)	1.01 (0.86-1.19)
Cervical cancer	498/1467	1.17 (0.88-1.54)	0.93 (0.73-1.19)
Bladder cancer	1252/2675	1.15 (0.95-1.39)	1.10 (0.96-1.27)
Central nervous system cancer	2214/3674	1.14 (0.97-1.34)	0.94 (0.85-1.03)
Uterine cancer	678/1902	1.10 (0.78-1.56)	0.89 (0.73-1.09)
Esophageal cancer	1899/2712	1.08 (0.92-1.27)	1.08 (0.96-1.22)
Kidney cancer	2041/4427	1.06 (0.91-1.23)	1.06 (0.95-1.17)
Pancreatic cancer	3176/4006	1.05 (0.92-1.19)	0.96 (0.88-1.04)
Sarcoma	2487/6244	1.01 (0.87-1.18)	1.03 (0.94-1.14)
Liver cancer	1478/1966	1.00 (0.82-1.21)	1.02 (0.90-1.16)
Colorectal cancer	3351/7500	0.95 (0.84-1.08)	1.03 (0.95-1.11)
Ovarian cancer	1125/2169	0.80 (0.62-1.03)	0.90 (0.78-1.04)

FIGURE 1 Smoking status, smoking intensity, age at initiation, and smoking cessation at cancer diagnosis with all-cause mortality in a prospective cohort of 128,423 cancer patients across 23 cancer types. (A) Kaplan-Meier survival estimates by smoking status. (B) Life expectancy by smoking status among male and female patients. (C-D) Effects of smoking amount (C) and age at initiation (D) among current smokers on the risk of death. (E) Effects of smoking cessation on the risk of death. (F) Association of smoking status with the risk of death by specific cancers

associations of smoking status with the risk of death were significant among most subgroups.

In this study, we assessed the benefits of smoking cessation prior to cancer diagnosis on the risk of death after cancer diagnosis, which has not been studied as comprehensively as that for smoking cessation after cancer diagnosis. We found that earlier smoking cessation prior to cancer diagnosis was associated with a greater reduction in the risk of death after cancer diagnosis in a dose-response manner, with long-term quitting approaching the risk reduction among never smokers, which strongly supports that it is never too late to stop smoking even for those who would develop cancer.

An interesting finding of our study was that the harms of current smoking and benefits of smoking cessation on mortality after cancer diagnosis were more evident for non-smoking-related cancers than for smoking-related cancers. One possible explanation is that, in our study, patients with non-smoking-related cancers on average survived longer than patients with smoking-related cancers, suggesting that the effects of current smoking and smoking cessation have a longer time to accumulate and are less likely to be dominated by the effects of a cancer diagnosis. Another interesting finding was that the prevalence of current smoking among patients with non-smoking-related cancers was high and close to that among patients with smoking-related cancers (9.7% *vs*. 13.8%). Future smoking cessation efforts should be directed at not only smoking-related cancers but also non-smoking-related cancers.

Our study has several strengths. It was a large prospective cohort study among cancer patients with comprehensive epidemiological and clinical data and long-term follow-up data, and we were able to adjust for a long list of potential confounders. Second, the dose-response relationship between the harms of current smoking and the benefits of smoking cessation was assessed. Additionally, we simultaneously studied a broad-spectrum of 23 specific cancers, with each cancer represented by at least 1000 cases. Finally, the treatment strategies were standardized and few individuals were lost to follow-up. We also acknowledge several potential limitations. Some current smokers at cancer diagnosis might quit smoking later, which might lead to underestimation of the risk associated with current smoking. Second, we cannot exclude the possibility that some of the observed association/effect is due to residual confounding from misclassification of the adjusted confounders that were self-reported or related to unmeasured factors. Third, when generalizing the prevalence of current or former smokers in cancer patients to other populations in the US or other countries/regions, caution should be taken due to different smoking and cessation rates in different populations. Meanwhile, the associations of smoking status, smoking intensity, age at initiation, and smoking cessation at cancer diagnosis with all-cause mortality observed in this study should be generalizable to other populations in the US or other countries/regions. Four, information on household income is not available in this dataset.

In summary, our study provided strong evidence showing significant harms of current smoking and benefits of smoking cessation on survival after cancer diagnosis across cancer types, especially non-smoking-related cancers. These findings support the development of evidence-based smoking cessation services to promote a difficult but important behavior change.

DECLARATIONS

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was approved by The University of Texas MD Anderson Cancer Center institutional review board (permit number: PA11-0929). Informed consent was obtained or waived to authorize data processing and analysis.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

Data used in this study are maintained by the MD Anderson Cancer Center (https://www.mdanderson.org/). Data requests are subject to approval by the review committees.

COMPETING INTERESTS

The authors declare that they have no competing interests.

FUNDING INFORMATION

This work was supported in part by the State of Texas Tobacco Settlement Funds for Patient History Database, Key Laboratory of Intelligent Preventive Medicine of Zhejiang Province (2020E10004), Leading Innovative and Entrepreneur Team Introduction Program of Zhejiang (2019R01007), and Key Research and Development Program of Zhejiang Province (2020C03002).

AUTHOR CONTRIBUTIONS

Xifeng Wu contributed to the collection, assembly, and quality control of the data. Xifeng Wu and Huakang Tu were responsible for the conception and design of the study. Huakang Tu, Yuanqing Ye, Maosheng Huang, and Xifeng Wu designed the strategies of data analysis and conducted the statistical analysis. Xifeng Wu, Huakang Tu, Yuanqing Ye, Kunlin Xie, Wong-Ho Chow, and Hua Zhao interpreted the data. Huakang Tu and Xifeng Wu drafted

the manuscript. All authors revised it critically for important intellectual content and agreed to submit the report for publication.

ACKNOWLEDGEMENTS

Not applicable.

Huakang Tu[1,2,3]
Yuanqing Ye[2]
Maosheng Huang[2]
Kunlin Xie[2,4]
Wong-Ho Chow[2]
Hua Zhao[2,5]
Xifeng Wu[1,2,3,6]

[1]*Department of Big Data in Health Science School of Public Health, Center of Clinical Big Data and Analytics of The Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, Zhejiang 310058, P. R. China*
[2]*Department of Epidemiology, The University of Texas MD Anderson Cancer Center, Houston, TX 77054, USA*
[3]*The Key Laboratory of Intelligent Preventive Medicine of Zhejiang Province, Hangzhou, Zhejiang 310058, P.R. China*
[4]*Department of Liver Surgery & Liver Transplantation, West China Hospital, Sichuan University, Chengdu, Sichuan 610041, P. R. China*
[5]*Department of Family Medicine and Population Health, Virginia Commonwealth University, Richmond, VA 23284, USA*
[6]*Cancer Center, Zhejiang University, Hangzhou, Zhejiang 310058, P.R. China*

Correspondence

Xifeng Wu, Department of Big Data in Health Science School of Public Health, Center of Clinical Big Data and Analytics of The Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou 310058, Zhejiang, P. R. China.
Email: xifengw@zju.edu.cn

Huakang Tu, Department of Big Data in Health Science School of Public Health, Center of Clinical Big Data and Analytics of The Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou 310058, Zhejiang, P. R. China.
Email: huakangtu@zju.edu.cn

ORCID

Xifeng Wu https://orcid.org/0000-0001-5174-3769

REFERENCES

1. National Center for Chronic Disease P, Health Promotion Office on S, Health. Reports of the Surgeon General. The Health Consequences of Smoking—50 Years of Progress: A Report of the Surgeon General. Atlanta (GA): Centers for Disease Control and Prevention (US); 2014.
2. Liu X, Yu Y, Wang M, Mubarik S, Wang F, Wang Y, et al. The mortality of lung cancer attributable to smoking among adults in China and the United States during 1990-2017. Cancer Commun (Lond). 2020;40(11):611–9.
3. Underwood JM, Townsend JS, Stewart SL, Buchannan N, Ekwueme DU, Hawkins NA, et al. Surveillance of demographic characteristics and health behaviors among adult cancer survivors–Behavioral Risk Factor Surveillance System, United States, 2009. MMWR Surveill Summ. 2012;61(1):1–23.
4. Agaku IT, King BA, Dube SR. Current cigarette smoking among adults - United States, 2005-2012. MMWR Morb Mortal Wkly Rep. 2014;63(2):29–34.
5. Tseng TS, Lin HY, Moody-Thomas S, Martin M, Chen T. Who tended to continue smoking after cancer diagnosis: the national health and nutrition examination survey 1999-2008. BMC Public Health. 2012;12:784.
6. Anderson CM, Yip R, Henschke CI, Yankelevitz DF, Ostroff JS, Burns DM. Smoking cessation and relapse during a lung cancer screening program. Cancer Epidemiol Biomarkers Prev. 2009;18(12):3476–83.
7. Foerster B, Pozo C, Abufaraj M, Mari A, Kimura S, D'Andrea D, et al. Association of Smoking Status With Recurrence, Metastasis, and Mortality Among Patients With Localized Prostate Cancer Undergoing Prostatectomy or Radiotherapy: A Systematic Review and Meta-analysis. JAMA Oncol. 2018;4(7):953–61.
8. Duan W, Li S, Meng X, Sun Y, Jia C. Smoking and survival of breast cancer patients: A meta-analysis of cohort studies. Breast. 2017;33:117–24.
9. Parsons A, Daley A, Begh R, Aveyard P. Influence of smoking cessation after diagnosis of early stage lung cancer on prognosis: systematic review of observational studies with meta-analysis. Bmj. 2010;340:b5569.
10. Walter V, Jansen L, Hoffmeister M, Brenner H. Smoking and survival of colorectal cancer patients: systematic review and meta-analysis. Ann Oncol. 2014;25(8):1517–25.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.