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RAPID COMMUNICATIONS

Smoking habit change after cancer diagnosis: effect on cardiovascular risk

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Introduction

Cancer survivors are rapidly increasing.[1] There is a need for strategies against cardiovascular disease (CVD), the leading cause of death after surviving cancer.[2] Despite the well-known adverse health effects of tobacco use, ~20% of individuals diagnosed with cancer smoke persistently after the diagnosis.[3,4] Yet, data are scarce regarding patterns and cardiovascular consequences of post-diagnosis smoking habit change among cancer survivors.

Methods

From a nationwide, single-provider database of the Korean National Health Insurance Service,[5] we identified 1 246 958 adults aged ≥20 newly diagnosed with cancer (having International Classification of Diseases, 10th revision [ICD-10] codes C00-C97 and critical condition code V193 for cancer)[6] in 2006–13. Among 864 840 (69.4%) 3-year survivors, 320 353 underwent health examination each within 2 years before and within 3 years after cancer diagnosis. After excluding 3273 participants with missing data on covariables and 7985 with CVD event before the date of 3-year survival (index date), a final study cohort of 309 095 participants remained. This study complied with the Declaration of Helsinki and was approved by the Institutional Review Board of Severance Hospital, Seoul, Korea (Y-2021-0052) with a waiver of informed consent.

Smoking status was assessed by a self-reported questionnaire during each of the last examination within 2 years before cancer (Exam 1) and the last examination within 3 years after cancer (Exam 2). Participants were categorized into four groups according to changes in smoking habits between Exams 1 and 2: (i) those who were not smoking in both exams were classified as 'sustained non-smokers'; (ii) those who were smoking in Exam 1 but were not smoking in Exam 2 were classified as 'quitters'; (iii) those who were not smoking in Exam 1 but were smoking in Exam 2 were classified as 'initiators or relapsers'; and (iv) those who were smoking in both exams were classified as 'continuing smokers'. The median (interquartile range) time interval between Exam 1 and cancer diagnosis was 0.5 (0.1–1.0) years, and that between cancer diagnosis and Exam 2 was 2.0 (1.6–2.5) years. The observed smoking habit changes were thereby considered to have occurred after cancer diagnosis.

The primary outcome was a composite CVD event, defined as the first hospitalization for myocardial infarction (ICD-10: I21-I23) or stroke (ICD-10: I60-I64), or cardiovascular death (ICD-10: I00-I99) by 31 December 2019. Cumulative incidence of CVD events was estimated using subdistribution cumulative incidence function, accounting for a competing risk of non-cardiovascular death.[7,8] Hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) were calculated using cause-specific Cox proportional hazards models, censoring participants at competing death events.[8] Analyses used SAS 9.4 (SAS Institute Inc., Cary, NC, USA) and R 4.0.3 (R Foundation, Vienna, Austria).

Results

Of the 309 095 cancer survivors (median age, 59 years; 51.8% women), 250 102 (80.9%) sustained non-smoking, 31 121 (10.1%) quit smoking,

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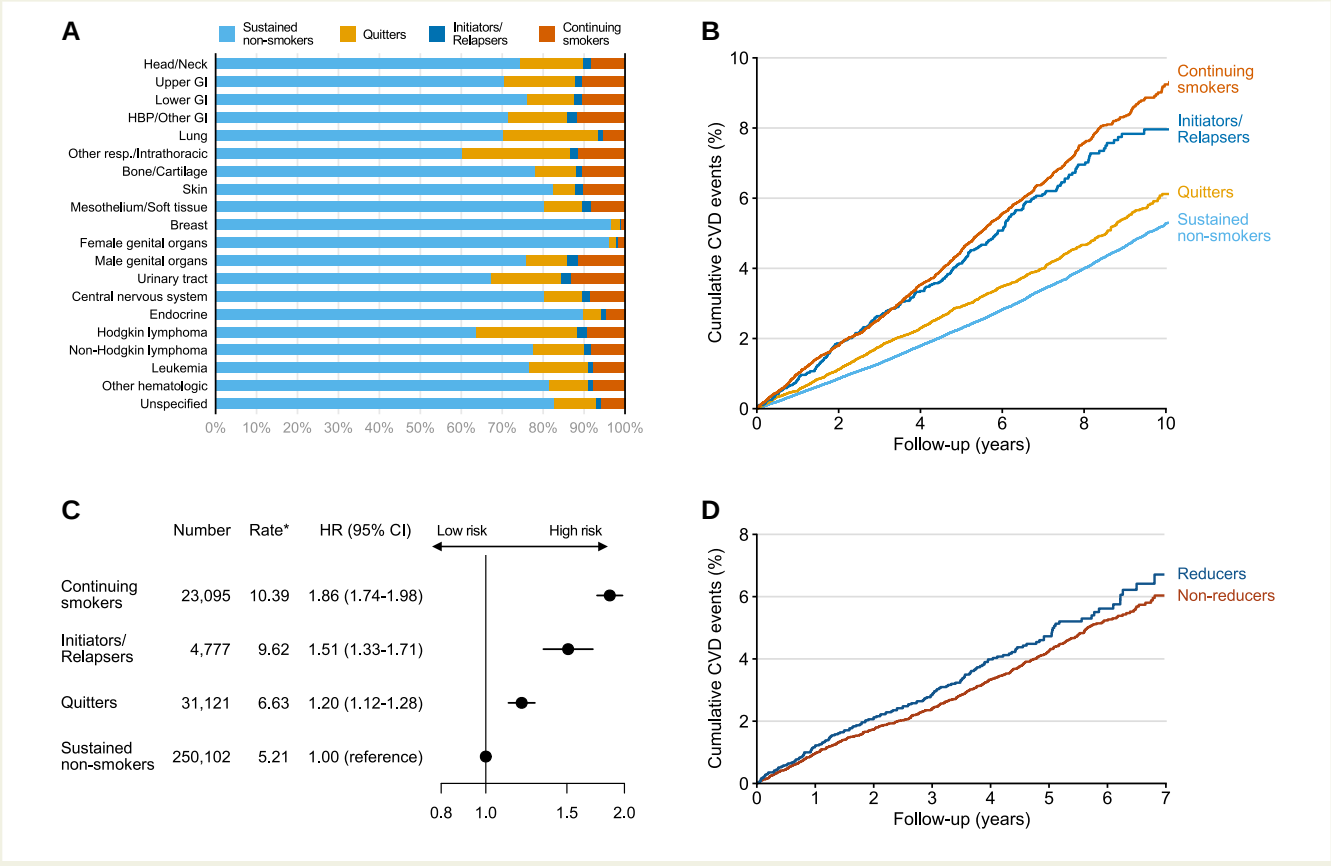

Figure 1 Post-diagnosis smoking habit change and incident cardiovascular disease events among cancer survivors. *(A)* Patterns of smoking habit change according to cancer type. *(B)* Cumulative incidence of cardiovascular disease events according to smoking habit change. *(C)* Risk of cardiovascular disease events according to smoking habit change. Hazard ratios were adjusted for age, sex, household income quartile, residential area, alcohol consumption, physical activity, body mass index (kg/m^2; <18.5, 18.5–22.9, 23–24.9, and ≥25), systolic blood pressure, fasting glucose, total cholesterol, blood pressure-lowering drug use, glucose-lowering drug use, lipid-lowering drug use, Charlson comorbidity index (0, 1, 2, and ≥3), cancer type, presence of distant metastasis at initial diagnosis, year of cancer diagnosis, chemotherapy regimen, and radiotherapy use. We placed fourth-order polynomials on age and fasting glucose, cubic terms on systolic blood pressure, and quadratic terms on total cholesterol. Data on chemotherapy regimen and radiotherapy use were updated during follow-up and modelled as time-varying covariables. *Incidence rate per 1000 person-years. *(D)* Cumulative incidence of cardiovascular disease events among smoking reducers vs. non-reducers. CI, confidence interval; CVD, cardiovascular disease; GI, gastrointestinal; HBP, hepatobiliary and pancreatic; HR, hazard ratio.

4777 (1.5%) initiated or relapsed to smoking, and 23 095 (7.5%) continued smoking after their respective cancer diagnoses. Patterns of smoking habit change varied across cancer types; the proportion of initiators/relapsers and continuing smokers combined was the highest among urinary tract (15.6%), male genital organ (14.2%), and hepatobiliary/pancreatic/other gastrointestinal (14.1%) cancer survivors, and was the lowest among breast (1.0%), female genital organ (2.1%), endocrine (5.7%), and lung (6.5%) cancer survivors (*Figure 1A*).

During a median follow-up of 5.5 years, 10 255 new CVD events occurred. The cumulative incidence of CVD events was the highest among continuing smokers, followed by initiators/relapsers, quitters, and sustained non-smokers (*Figure 1B*). When sustained non-smokers were the reference, multivariable-adjusted HRs (95% CIs) for CVD events were 1.20 (1.12–1.28) among quitters, 1.51 (1.33–1.71) among initiators/relapsers, and 1.86 (1.74–1.98) among continuing smokers (*Figure 1C*). When compared with continuing smokers, multivariable-adjusted HR (95% CI) for CVD events was 0.64 (0.59–0.70) among quitters.

The findings were consistent for all individual components of the primary outcome and across both sexes. When the study participants were classified according to their first primary cancers,[6] the results were broadly similar across all cancer types. However, the analyses were underpowered to draw definitive conclusions for certain types of cancer (e.g. bone/cartilage, soft tissue, or haematologic cancer).

Among 15 392 continuing smokers with data on tobacco consumption per day, 3105 (20.2%) reduced their daily tobacco intake by ≥50% after cancer diagnosis. Smoking reduction without cessation was not associated with a lower risk of CVD events (multivariable-adjusted HR 0.99, 95% CI 0.80–1.22) (*Figure 1D*).

Discussion

Over 40% of smokers in our study opted to continue smoking even after cancer diagnosis (*Graphical Abstract*). This calls for additional efforts to promote smoking cessation among cancer survivors, preferably during

immediate post-diagnostic period with the highest motivation for smoking cessation.[9] On the other hand, ~2% of non-smokers initiated or relapsed to smoking after cancer diagnosis (*Graphical Abstract*). As cancer survivors can gradually lose their motivation for maintaining a healthy lifestyle after recovery,[4] tobacco prevention support for non-smoking survivors should continue throughout the whole survivorship phase.

This study contributes to the field in three distinctive aspects. First, our demonstration of the differing patterns of smoking habit change by cancer type emphasizes the importance of developing cancer type-specific strategies for tobacco control. Second, our research extends the findings from the general population to cancer survivors who may gain cardiovascular benefits from smoking cessation and be harmed by smoking initiation/relapse. Third, our analysis offers new insights into the potential limitations of smoking reduction as a measure to reduce CVD risk among patients with cancer.[10] Overall, our findings provide the first specific evidence to inform tobacco control programs for cancer survivors, which have primarily relied on evidence obtained from non-cancer populations.[9]

Study limitations include (i) the use of self-reported questionnaire for smoking status assessment; (ii) the possibility of residual confounding; (iii) the potential crossover of the participants during follow-up; and (iv) the uncertainty in the generalizability of the findings, especially to those who did not participate in serial health examinations and were excluded from the study. Nevertheless, the substantiated high rate of smoking after cancer diagnosis and its association with CVD events highlight the urgent need for initiatives to promote smoking cessation and prevent smoking initiation/relapse among patients with cancer.

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Data availability

Because of the sensitive nature of the database, requests to access the data from qualified researchers may be sent to the National Health Insurance Service at https://nhiss.nhis.or.kr.

Conflict of interest

D.L.B. discloses the following relationships—Advisory Board: AngioWave, Bayer, Boehringer Ingelheim, Cardax, CellProthera, Cereno Scientific, Elsevier Practice Update Cardiology, High Enroll, Janssen, Level Ex, McKinsey, Medscape Cardiology, Merck, MyoKardia, NirvaMed, Novo Nordisk, PhaseBio, PLx Pharma, Regado Biosciences, Stasys; Board of Directors: AngioWave (stock options), Boston VA Research Institute, Bristol Myers Squibb (stock), DRS.LINQ (stock options), High Enroll (stock), Society of Cardiovascular Patient Care, TobeSoft; Chair: Inaugural Chair, American Heart Association Quality Oversight Committee; Consultant: Broadview Ventures; Data Monitoring Committees: Acesion Pharma, Assistance Publique-Hôpitaux de Paris, Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute, for the PORTICO trial, funded by St. Jude Medical, now Abbott), Boston Scientific (Chair, PEITHO trial), Cleveland Clinic (including for the ExCEED trial, funded by Edwards), Contego Medical (Chair, PERFORMANCE 2), Duke Clinical Research Institute, Mayo Clinic, Mount Sinai School of Medicine (for the ENVISAGE trial, funded by Daiichi Sankyo; for the ABILITY-DM trial, funded by Concept Medical), Novartis, Population Health Research Institute; Rutgers University (for the NIH-funded MINT Trial); Honoraria: American College of Cardiology (Senior Associate Editor, Clinical Trials and News, ACC.org; Chair, ACC Accreditation Oversight Committee), Arnold and Porter law firm (work related to Sanofi/Bristol-Myers Squibb clopidogrel litigation), Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute; RE-DUAL PCI clinical trial steering committee funded by Boehringer Ingelheim; AEGIS-II executive committee funded by CSL Behring), Belvoir Publications (Editor in Chief, Harvard Heart Letter), Canadian Medical and Surgical Knowledge Translation Research Group (clinical trial steering committees), Cowen and Company, Duke Clinical Research Institute (clinical trial steering committees, including the PRONOUNCE trial, funded by Ferring Pharmaceuticals), HMP Global (Editor in Chief, Journal of Invasive Cardiology), Journal of the American College of Cardiology (Guest Editor; Associate Editor), K2P (Co-Chair, interdisciplinary curriculum), Level Ex, Medtelligence/ReachMD (CME steering committees), MJH Life Sciences, Oakstone CME (Course Director, Comprehensive Review of Interventional Cardiology), Piper Sandler, Population Health Research Institute (for the COMPASS operations committee, publications committee, steering committee, and US national co-leader, funded by Bayer), Slack Publications (Chief Medical Editor, Cardiology Today's Intervention), Society of Cardiovascular Patient Care (Secretary/Treasurer), WebMD (CME steering committees), Wiley (steering committee); Other: Clinical Cardiology (Deputy Editor), NCDR-ACTION Registry Steering Committee (Chair), VA CART Research and Publications Committee (Chair); Patent: Sotagliflozin (named on a patent for sotagliflozin assigned to Brigham and Women's Hospital who assigned to Lexicon; neither I nor Brigham and Women's Hospital receive any income from this patent); Research Funding: Abbott, Acesion Pharma, Afimmune, Aker Biomarine, Amarin, Amgen, AstraZeneca, Bayer, Beren, Boehringer Ingelheim, Boston Scientific, Bristol-Myers Squibb, Cardax, CellProthera, Cereno Scientific, Chiesi, CinCor, CSL Behring, Eisai, Ethicon, Faraday Pharmaceuticals, Ferring Pharmaceuticals, Forest Laboratories, Fractyl, Garmin, HLS Therapeutics, Idorsia, Ironwood, Ischemix, Janssen, Javelin, Lexicon, Lilly, Medtronic, Merck, Moderna, MyoKardia, NirvaMed, Novartis, Novo Nordisk, Owkin, Pfizer, PhaseBio, PLx Pharma, Recardio, Regeneron, Reid Hoffman Foundation, Roche, Sanofi, Stasys, Synaptic, The Medicines Company, Youngene, 89Bio; Royalties: Elsevier (Editor, Braunwald's Heart Disease); Site Co-Investigator: Abbott, Biotronik, Boston Scientific, CSI, Endotronix, St. Jude Medical (now Abbott), Philips, SpectraWAVE, Svelte, Vascular Solutions; Trustee: American College of Cardiology; Unfunded Research: FlowCo, Takeda. All other authors declare that there is no conflict of interest relevant to this work.

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