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E-cigarette switching in COPD: reduced cardiovascular events without improvement in respiratory outcomes

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Abstract

Background The impact of switching to e-cigarettes in smokers after a chronic obstructive pulmonary disease (COPD) diagnosis on long-term health outcomes has not been widely evaluated.

Methods This nationwide cohort included 23,262 adults aged 40–80 years who were current smokers at the time of COPD diagnosis between 2016 and 2023. Based on follow-up health screening data, patients were categorized as continued smokers, quitters, or e-cigarette users (including dual users). The outcomes included lung cancer, COPD exacerbations, major adverse cardiac and cerebrovascular events (MACCE), and all-cause mortality. Adjusted hazard ratios (aHRs) with 95% confidence intervals (CIs) were estimated using Cox proportional hazards model.

Results Among 23,262 patients with COPD, 14,899 (64.0%) continued smoking, 7,047 (30.3%) quit, and 1,316 (5.7%) switched to e-cigarettes. During follow-up, quitters had significantly lower risks of lung cancer (adjusted HR [aHR], 0.85; 95% CI, 0.72–0.99), COPD exacerbations (aHR, 0.90; 95% CI, 0.84–0.97), MACCE (aHR, 0.85; 95% CI, 0.79–0.93), and all-cause mortality (aHR, 0.90; 95% CI, 0.82–0.99) compared with continued smokers. Switching to e-cigarettes was not associated with a lower risk of lung cancer (aHR, 0.94; 95% CI, 0.65–1.37) or COPD exacerbations (aHR, 0.98; 95% CI, 0.84–1.14) but was associated with a reduced risk of MACCE (aHR, 0.80; 95% CI, 0.66–0.97).

Conclusions Complete smoking cessation was associated with lower risks of lung cancer, COPD exacerbations, MACCE, and all-cause mortality. In contrast, switching to e-cigarettes was associated with a reduced risk of MACCE but did not provide comparable respiratory benefits.

Keywords COPD, E-cigarette, Smoking, Lung cancer, Exacerbation, Cardiovascular disease

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Background

Chronic obstructive pulmonary disease (COPD) remains the third leading cause of mortality worldwide in 2023, representing a significant global health burden [1]. While complete smoking cessation is the most effective intervention to slow disease progression and reduce the risks of lung cancer, acute exacerbations, and premature death [2], many patients struggle to achieve smoking cessation following a COPD diagnosis [3]. This challenge has fueled interest in electronic cigarettes (e-cigarettes) as potential harm-reduction tools [4, 5]. Nevertheless, the rate of complete smoking cessation remains low, with only about 18% of smokers who switch to e-cigarettes achieving full cessation [6].

Additionally, the long-term health effects of e-cigarettes remain controversial [7]. In studies on healthy adults, e-cigarette use has been associated with ventilation impairment and abnormalities in lung function and diffusion capacity [8, 9]. Population-based studies have suggested that e-cigarettes are associated with an increased risk of chronic respiratory disorders such as asthma and COPD [10, 11]. However, risk estimates derived from a healthy population may not be generalizable to individuals with pre-existing chronic diseases [7, 12]. For instance, among smokers who had undergone intervention for coronary artery disease, switching to e-cigarettes was associated with a lower risk of major cardiovascular events than in those who continued smoking [13]. Whether these potential benefits extend to patients with COPD as a form of lifestyle modification after diagnosis remains unclear. Although recent studies involving several dozen patients with COPD who switched to e-cigarettes have reported improvements in exacerbations, respiratory parameters, and quality of life, the small sample size and absence of a control group limit the generalizability of these findings [14, 15]. To date, large-scale population-based studies assessing the long-term outcomes of switching to e-cigarettes following COPD diagnosis are lacking.

Therefore, we conducted a nationwide cohort study on patients newly diagnosed with COPD who were current smokers at the time of diagnosis. This study aimed to evaluate the association between post-diagnosis smoking behaviors, including complete cessation, switching to e-cigarettes, and continued cigarette smoking, and the subsequent risks of lung cancer, all-cause mortality, COPD exacerbation, and cardiovascular outcomes.

Methods

Data sources and study population

This retrospective cohort study used data from the Korean National Health Insurance System (NHI) database, which covers the entire Korean population [16]. The K-NHIS database contains comprehensive data on demographics, healthcare utilization, diagnoses based on ICD-10 codes, procedures, prescription medications, and standardized biennial health screening examination results. Health-screening data included detailed questionnaires on smoking and alcohol use, physical activity, comorbidities, anthropometric measurements, and laboratory findings. Participation in the national health-screening program exceeded 75% of the eligible adults in Korea.

We identified individuals aged 40–80 years who were diagnosed with chronic obstructive pulmonary disease (COPD), defined as the presence of ICD-10 codes J43 or J44 (excluding J43.0), with a prescription for COPD medications at least twice within a year. The COPD medications included long-acting muscarinic antagonists (LAMAs), long-acting beta-2 agonists (LABAs), inhaled corticosteroids (ICS) combined with LABA, short-acting muscarinic antagonists (SAMAs), short-acting beta-2 agonists (SABAs), methylxanthines, systemic beta agonists, and phosphodiesterase-4 (PDE-4) inhibitors [17–19]. Prescriptions issued within 30 days were considered part of the same treatment episode and were not counted as separate prescriptions.

Among the eligible patients, we included only those whose initial COPD treatment occurred between January 1, 2016, and December 31, 2023, and who had completed at least one health screening examination before (Exam 1) and after (Exam 2) the date of COPD diagnosis. To focus on the impact of smoking reduction and cessation after a COPD diagnosis, we restricted the study population to individuals who reported being current smokers in Exam 1 ($N = 62,259$). Among them, only patients with follow-up health examination data within 3 years of COPD diagnosis (Exam 2) were included ($N = 32,004$). Patients were excluded if they had a history of cancer before Exam 2. To further minimize reverse causality, individuals who developed cancer or died within the first six months after Exam 2 were excluded ($N = 8,742$). The final analytical cohort consisted of 23,262 participants (Supplementary Fig. 1).

This study was approved by the Institutional Review Board of the Samsung Medical Center (IRB No. SMC 2024-03-120). The requirement for informed consent was waived due to the use of de-identified administrative data. All study procedures were conducted in accordance with relevant guidelines and regulations, including the Declaration of Helsinki.

Outcome measurements

Pulmonary outcomes included the incidence of lung cancer and COPD exacerbations. Lung cancer was defined as the presence of a cancer-specific insurance claims code (V193) with a C33 or C34 code, which is the ICD-10 code for lung cancer. In Korea, once a person receives a cancer

diagnosis, he or she is registered with the National Cancer Registry with a specific code that indicates the system in which the person has been diagnosed with cancer and is receiving special insurance benefits.

Moderate exacerbation of COPD after diagnosis was defined as an outpatient visit with ICD-10 J43.X (except J43.0) or J44.X and a prescription for systemic steroids or antibiotics on the same visit. Severe exacerbation of COPD after diagnosis was defined as in-patient or emergency room visit with one of the following ICD-10 codes as the principal or secondary diagnosis: COPD (J43.X [except J43.0] or J44.X) or COPD-related disease (pneumonia [J12.X–J17.X], pulmonary thromboembolism [I26, I26.0, or I26.9], dyspnea [R06.0], or acute respiratory distress syndrome [J80]), and a prescription for systemic steroids or antibiotics at the same visit [19].

We also evaluated the major adverse cardiac and cerebrovascular events (MACCE), defined as a composite of death from any cause, myocardial infarction (MI), revascularization, and ischemic stroke. The vital status and cause of death were obtained from death certificates collected by Statistics Korea at the Ministry of Strategy and Finance of South Korea [16]. MI was defined as the presence of the diagnostic codes ICD-10, I21, or I22 in the primary position during hospitalization with procedure codes for percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG). In a validation study, the accuracy of MI diagnosis using the Korean NHIS data was 93% [20]. Revascularization was defined as the presence of a procedure code for PCI or CABG after the study index date. Ischemic stroke was defined based on ICD codes for ischemic stroke (ICD-10 I63, I64, or G45) combined with codes for diagnostic brain imaging, such as magnetic resonance imaging or perfusion computed tomography.

Assessment of smoking habits

Smoking status and history were assessed using a structured self-report questionnaire during routine health screening examinations. All participants included in the study reported smoking within 3 years prior to the diagnosis of COPD (Exam 1). Changes in smoking status were evaluated using a questionnaire in Exam 2, performed within 3 years of diagnosis (Supplementary Fig. 2). Participants were asked about their lifetime and current use of combustible cigarettes and e-cigarettes, the frequency and intensity of cigarette use (packs per day), and the duration of smoking.

The study participants were categorized into three groups based on their reported behavior after the COPD diagnosis: (1) continued combustible cigarette users (defined as those who continued to use only combustible cigarettes), (2) successful quitters (defined as those who reported no current use of either combustible cigarettes or e-cigarettes), and (3) users switched to e-cigarette (defined as those who reported any current use of e-cigarettes, regardless of continued use of combustible cigarettes). Because these categories reflect ordered levels of reduction in combustible cigarette consumption, comparisons across exposure groups were used to evaluate gradients of smoking reduction. Exclusive e-cigarette use versus continued combustible cigarette use was prespecified as a co-primary exposure contrast. For sensitivity analyses, participants who used both combustible cigarettes and e-cigarettes were defined as dual users, while those who reported exclusive use of e-cigarettes without concurrent combustible cigarette use were categorized as exclusive e-cigarette users.

Covariables

Information on the residential area and household income was obtained from insurance eligibility records. Residential areas were classified as metropolitan (Seoul, Busan, Daegu, Daejeon, Gwangju, Incheon, and Ulsan) or non-metropolitan. Income was categorized as Medical Aid, ≤ 30th percentile, 31st–70th percentile, or > 70th percentile. Data on alcohol consumption, physical activity, and body mass index (BMI) were obtained from Exam 2. The Charlson Comorbidity Index (CCI) was calculated using diagnosis codes from claims data from the year prior to the study index date [21]. The ICD-10 codes used for each CCI component are provided in Supplementary Table 1.

Statistical analysis

Baseline characteristics are reported as means ± standard deviation, median (interquartile range), or number (%), as appropriate. The standardized mean difference (SMD) between groups was estimated to compare the distribution of variables. SMDs were calculated pairwise across exposure groups, and the maximum absolute value was reported.

The primary analysis evaluated the clinical outcomes across three exposure groups, using continued combustible cigarette smokers as the reference category. Furthermore, a co-primary analysis was conducted to compare exclusive e-cigarette users (those who switched completely without concurrent combustible cigarette use) directly with continued combustible cigarette smokers.

In this study, the cumulative incidence of lung cancer and mortality were calculated across subgroups. Hazard ratios (HRs) and the corresponding 95% confidence intervals (CIs) of the outcomes for each group were calculated using Cox proportional hazards models. The proportionality of the hazards was confirmed by visual inspection of the log-minus-log plots and Schoenfeld residuals.

All multivariate models were adjusted for covariates measured at Exam 2, including socio-demographics (age,

sex, residential area, household income), lifestyle factors (alcohol consumption, regular physical activity, cumulative smoking exposure measured by pack-years), and clinical history [initial COPD treatment regimen (LABA, LAMA, or ICS use), history of pneumonia in the previous year, and history of severe exacerbation in the previous year] as a priori selected covariates known to be associated with both exposure and outcomes. Missing values for covariates were handled by including an explicit "Unknown" category, rather than excluding participants or imputing missing values. No imputation procedures were applied. Additionally, we used the fine-and-gray method to calculate the sub-distribution hazard ratios (subHRs) for the incidence of lung cancer to account for competing risks due to mortality [22].

Furthermore, stratified analyses were conducted to evaluate whether switching to e-cigarettes was associated with lung cancer across the specified subgroups. These subgroups included age (< 65 vs. ≥65), sex (male vs. female), history of severe exacerbation in the previous year, CCI (0–1 vs. ≥2), smoking status at Exam 1 (< 30 vs. ≥ 30 pack years), and use of ICS. We selected these subgroups based on previous literature suggesting that they may be affected by physical activity in reducing mortality [19].

We conducted several sensitivity analyses to assess the robustness of the findings. First, analyses were repeated after restricting the cohort to participants whose Exam 2 occurred within 12 months of COPD diagnosis to reduce potential heterogeneity in exposure timing. Second, to minimize potential bias from adjustment for post-exposure variables, we performed additional multivariable Cox models adjusted only for baseline covariates measured prior to COPD diagnosis. Third, we conducted a propensity score–matched analysis to address potential residual confounding and to focus on the most policy-relevant comparison. This analysis was restricted to continued combustible cigarette users and participants who switched to e-cigarette use, excluding successful quitters. Propensity scores were estimated using a multivariable logistic regression model including age, sex, residential area, household income, alcohol consumption, regular physical activity, cumulative smoking exposure measured by pack-years, initial COPD treatment regimen, history of pneumonia in the previous year, and history of severe exacerbation in the previous year. Participants were matched using a nearest-neighbor algorithm with a caliper of 0.2 of the standard deviation of the logit of the propensity score. Covariate balance after matching was assessed using standardized mean differences, with values less than 0.1 indicating adequate balance. Fourth, sensitivity analyses were conducted restricting the cohort to individuals who maintained their reported smoking category at subsequent follow-up examinations.

All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) and R version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Among the 23,262 patients with COPD who smoked before COPD, smoking change at Exam 2 occurred at a median of 1.0 year after diagnosis, at which time, 14,899 continued smoking combustible cigarettes, 7,047 successfully quit smoking, and 1,316 switched to e-cigarettes after COPD. Among the switching to e-cigarettes group, 393 participants reported complete switching to e-cigarettes without concurrent use of combustible cigarettes. Those who switched to e-cigarettes were most likely to be the youngest, have the highest body mass index, highest proportion of residents in metropolitan areas, and have the highest income category (Table 1). However, the distribution of respiratory diseases and laboratory and clinical characteristics did not differ substantially between groups.

In terms of smoking status prior to COPD diagnosis, all study participants were current smokers. The proportion of individuals with a smoking history of 30 pack-years or more was greatest among continued combustible cigarette users, while the number of combustible cigarettes consumed before COPD diagnosis was similar between continued users and those who later switched to e-cigarettes. At Exam 2, participants who switched to e-cigarette use showed a substantial reduction in the number of combustible cigarettes smoked per day compared with continued combustible cigarette users (Table 1).

Median follow-up time from Exam 2 was 4.6 years [interquartile range (IQR), 3.6–5.2] for continued combustible cigarette users, 4.6 years [3.5–5.2] for successful quitters, and 5.1 years [4.5–5.5] for e-cigarette users. The cumulative five-year incidence of lung cancer was 3.9% among continued combustible cigarette users, 3.8% among successful quitters, and 2.7% among those who switched to e-cigarettes (Fig. 1). After adjustment for relevant covariates, successful quitting was associated with a significantly reduced risk of lung cancer compared to continued cigarette smoking (adjusted hazard ratio (aHR) = 0.85; 95% confidence interval (CI) 0.72, 0.99). In contrast, switching to e-cigarettes was not associated with a significant reduction in lung cancer risk compared with continued cigarette smoking (aHR = 0.94; 95% CI = 0.65, 1.37, Table 2). There was also no statistically significant decrease in lung cancer risk between exclusive e-cigarette users and continued combustible cigarette users (Table 3).

Subgroup analyses showed consistent results across the strata. The association between switching to e-cigarettes and the reduced risk of lung cancer was more evident in

Table 1 Patient characteristics

	Continued combustible cigarette users (*N* = 14,899)	Successful quitters (*N* = 7,047)	Users switched to e-cigarette (*N* = 1,316)	SMD
Age, years	64.2 (8.7)	66.2 (8.5)	57.3 (9.4)	>0.999
Sex, male	13,581 (91.2)	6,368 (90.4)	1,233 (93.7)	0.123
Body mass index, kg/m^2	23.48 (3.50)	23.93 (3.35)	24.51 (3.61)	0.290
Residential area, metropolitan	8,301 (55.7)	3,923 (55.7)	881 (66.9)	0.233
Income				
Medical Aid	1,068 (7.2)	379 (5.4)	47 (3.6)	0.160
≤ 30th	3,652 (24.5)	1,597 (22.7)	285 (21.7)	0.068
31st – 70th	5,253 (35.3)	2,489 (35.3)	406 (30.9)	0.095
> 70th	4,722 (31.7)	2,493 (35.4)	565 (42.9)	0.234
Unknown	204 (1.4)	89 (1.3)	13 (1.0)	0.035
Prior comorbidities				
Charlson comorbidity index	2.14 (1.57)	2.25 (1.66)	1.89 (1.50)	0.228
Diabetes mellitus	4,222 (28.3)	2,055 (29.2)	276 (21.0)	0.190
Hypertension	6,986 (46.7)	3,608 (51.2)	496 (37.7)	0.274
Dyslipidemia	7,480 (50.2)	3,822 (54.2)	582 (44.2)	0.201
Pneumonia	2,060 (13.8)	1,315 (18.7)	178 (13.5)	0.140
Smoking pack year in Exam 1, ≥ 30 packs/year	7,436 (49.9)	3,004 (42.6)	569 (43.1)	0.146
Number of combustible cigarettes in Exam 1, packs/day	17.09 (7.95)	15.19 (7.64)	17.79 (7.99)	0.333
Number of combustible cigarettes in Exam 2, packs/day	15.67 (7.90)	0	12.80 (10.09)	0.317
Other habits in Exam 2				
Current drinker, yes	9,071 (60.9)	3,487 (49.5)	947 (72.0)	0.473
Regular physical activity, yes	4,184 (28.1)	2,223 (31.5)	335 (25.5)	0.135
Laboratory findings in Exam 2				
Fasting glucose, mg/dL	106.90 (29.09)	106.57 (25.98)	106.43 (26.82)	0.017
Total cholesterol, mg/dL	184.21 (41.83)	184.96 (42.75)	192.13 (45.12)	0.182
HDL cholesterol, mg/dL	52.45 (14.49)	52.86 (14.32)	52.87 (15.34)	0.028
LDL cholesterol, mg/dL	103.69 (41.35)	104.30 (38.25)	108.32 (39.50)	0.115
Vital sign in Exam 2				
Systolic blood pressure, mmHg	125.41 (14.75)	127.36 (14.90)	124.30 (13.80)	0.213
Diastolic blood pressure, mmHg	76.34 (9.81)	76.79 (9.74)	74.40 (9.63)	0.247
History of severe exacerbation	1,053 (7.1)	614 (8.7)	73 (5.5)	0.123
Initial treatment				
LABA/LAMA	4,478 (30.1)	2,343 (33.2)	303 (23.0)	0.229
LABA/LAMA + ICS	1,282 (8.6)	790 (11.2)	101 (7.7)	0.121
LABA or LAMA	2,635 (17.7)	1,264 (17.9)	221 (16.8)	0.030
LABA + ICS	6,439 (43.2)	2,620 (37.2)	686 (52.1)	0.304
LAMA + ICS	65 (0.4)	30 (0.4)	5 (0.4)	0.009

Values were presented as n (%) or mean (SD)

ICS Inhaled corticosteroids, *LABA* Long-acting beta-2 agonists, *LAMA* Long-acting muscarinic antagonist

older individuals, heavy smokers, and those who did not receive ICS. In contrast, no benefit was observed in participants with a greater comorbidity burden. (Fig. 2).

In terms of incidence of exacerbation rate, successful quitting was associated with a statistically significant reduction in the risk of moderate-to-severe exacerbation (aHR = 0.90; 95% CI, 0.84, 0.97) and severe exacerbation (aHR = 0.84; 95% CI, 0.75, 0.95) compared to continued cigarette smoking. Among those who switched to e-cigarettes, the risk of severe exacerbation was lower (aHR = 0.84; 95% CI, 0.63, 1.12), but the risk of moderate to severe exacerbation did not differ from continued combustible cigarette users (aHR = 0.98; 95% CI, 0.84, 1.14). These findings were consistent with the competing risk analyses (Table 2). In co-primary comparison between exclusive e-cigarette users and continued combustible cigarette users, the adjusted HR for moderate-to-severe exacerbation in the completed switching to e-cigarette group was 0.91 (0.67 to 1.22), and the adjusted HR for severe exacerbation was 0.78 (0.46 to 1.32) (Table 3).

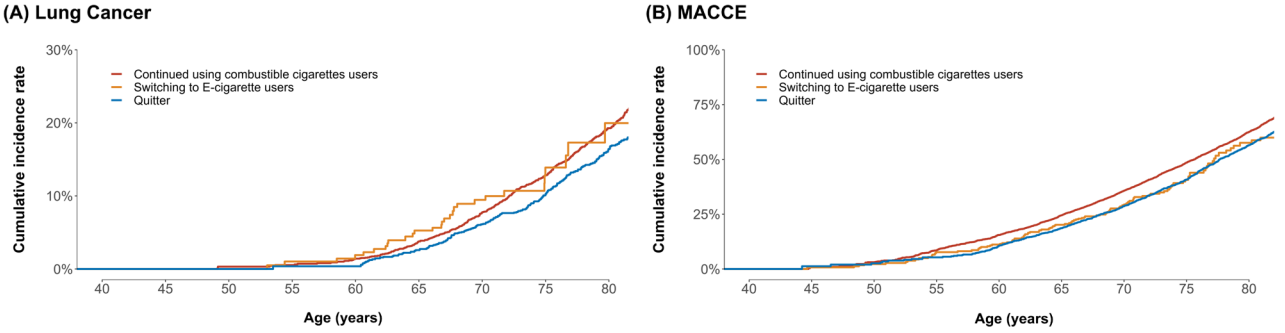


Fig. 1 Fine–Gray cumulative incidence curves for lung cancer accounting for the competing risk of death (**A**) and Kaplan–Meier cumulative incidence curves for major adverse cardiovascular and cerebrovascular events (MACCE) with age as the time scale (**B**)

Table 2 Comparative effectiveness of smoking behavior changes on lung cancer, exacerbation and cardiovascular outcomes

	Continued combustible cigarette users	Successful quitters	Users switched to e-cigarette
Lung cancer			
No. of cases (5 years cumulative incidence)	504 (3.9)	224 (3.8)	30 (2.7)
Adjusted HR (95% CI)	*Reference*	**0.85 (0.72, 0.99)**	0.94 (0.65, 1.37)
SubHR (95% CI)	*Reference*	**0.85 (0.72, 0.99)**	0.95 (0.66, 1.37)
Exacerbation			
Moderate-to-severe exacerbation			
No of cases (1 year incidence rate %)	2,621 (6.1)	1,232 (6.1)	195 (5.5)
Adjusted HR (95% CI)	*Reference*	**0.90 (0.84, 0.97)**	0.98 (0.84, 1.14)
SubHR (95% CI)	*Reference*	**0.90 (0.84, 0.97)**	0.99 (0.85, 1.15)
Severe exacerbation			
No of cases (1 year incidence rate %))	865 (1.4)	403 (1.5)	51 (1.2)
Adjusted HR (95% CI)	*Reference*	**0.84 (0.75, 0.95)**	0.84 (0.63, 1.12)
SubHR (95% CI)	*Reference*	**0.85 (0.75, 0.96)**	0.86 (0.64, 1.14)
Cardiovascular outcomes			
MACCE			
No. of cases (5 years cumulative incidence)	2,171 (16.4)	1,017 (16.3)	114 (8.7)
Adjusted HR (95% CI)	*Reference*	**0.85 (0.79, 0.93)**	**0.80 (0.66, 0.97)**
All-cause mortality			
No. of cases (5 years cumulative incidence)	1,279 (9.9)	657 (10.7)	62 (4.8)
Adjusted HR (95% CI)	*Reference*	**0.90 (0.82, 0.99)**	0.82 (0.63, 1.06)
Myocardial infarction			
No. of cases (5 years cumulative incidence)	210 (1.6)	75 (1.2)	8 (0.6)
Adjusted HR (95% CI)	*Reference*	**0.66 (0.51, 0.87)**	0.52 (0.26, 1.06)
SubHR (95% CI)	*Reference*	**0.66 (0.51, 0.87)**	0.52 (0.26, 1.06)
Revascularization			
No. of cases (5 years cumulative incidence)	547 (4.1)	213 (3.5)	32 (2.6)
Adjusted HR (95% CI)	*Reference*	**0.75 (0.63, 0.88)**	0.76 (0.53, 1.10)
SubHR (95% CI)	*Reference*	**0.75 (0.63, 0.88)**	0.76 (0.53, 1.10)
Ischemic stroke			
No. of cases (5 years cumulative incidence)	510 (4.0)	228 (3.6)	30 (2.3)
Adjusted HR (95% CI)	*Reference*	**0.82 (0.70, 0.97)**	0.87 (0.60, 1.27)
SubHR (95% CI)	*Reference*	**0.82 (0.70, 0.97)**	0.88 (0.61, 1.28)

Abbreviation: *MACCE* Major adverse cardiac and cerebrovascular events

Adjusted for covariates measured at Exam 2, including age, sex, residential area, household income, alcohol consumption, regular physical activity, cumulative smoking exposure measured by pack-years, initial COPD treatment regimen (LABA, LAMA, or ICS use), history of pneumonia in the previous year, and history of severe exacerbation in the previous year. Bold indicates statistical significance ($p < 0.05$)

*MACCE included death from any cause, myocardial infarction, revascularization, and ischemic stroke

Table 3 Comparative effectiveness of lung cancer, exacerbation, and cardiovascular outcome between exclusive e-cigarette users compared to the continued combustible cigarette users

	Continued combustible cigarette users	Exclusive e-cigarette users
Lung cancer		
No. of cases (5 years cumulative incidence)	504 (3.9)	10 (3.3)
Adjusted HR (95% CI)	*Reference*	1.03 (0.55, 1.92)
SubHR (95% CI)	*Reference*	1.03 (0.56, 1.92)
Exacerbation		
Moderate-to-severe exacerbation		
No of cases (1 year incidence rate %)	2,621 (6.1)	44 (3.8)
Adjusted HR (95% CI)	*Reference*	0.91 (0.67, 1.22)
SubHR (95% CI)	*Reference*	0.91 (0.67, 1.22)
Severe exacerbation		
No of cases (1 year incidence rate %))	865 (1.4)	14 (0.8)
Adjusted HR (95% CI)	*Reference*	0.78 (0.46, 1.32)
SubHR (95% CI)	*Reference*	0.78 (0.46, 1.32)
Cardiovascular outcomes		
MACCE*		
No. of cases (5 years cumulative incidence)	2,171 (16.4)	33 (8.4)
Adjusted HR (95% CI)	*Reference*	0.74 (0.52, 1.04)
All-cause mortality		
No. of cases (5 years cumulative incidence)	1,279 (9.9)	22 (6.5)
Adjusted HR (95% CI)	*Reference*	0.89 (0.59, 1.36)
Myocardial infarction		
No. of cases (5 years cumulative incidence)	210 (1.6)	0 (-)
Adjusted HR (95% CI)	*Reference*	-
SubHR (95% CI)	*Reference*	-
Revascularization		
No. of cases (5 years cumulative incidence)	547 (4.1)	6 (1.7)
Adjusted HR (95% CI)	*Reference*	0.48 (0.21, 1.07)
SubHR (95% CI)	*Reference*	0.48 (0.21, 1.07)
Ischemic stroke		
No. of cases (5 years cumulative incidence)	510 (4.0)	9 (1.7)
Adjusted HR (95% CI)	*Reference*	0.85 (0.44, 1.65)
SubHR (95% CI)	*Reference*	0.86 (0.44, 1.65)

Abbreviation: *MACCE* Major adverse cardiac and cerebrovascular events

Adjusted for covariates measured at Exam 2, including age, sex, residential area, household income, alcohol consumption, regular physical activity, cumulative smoking exposure measured by pack-years, initial COPD treatment regimen (LABA, LAMA, or ICS use), history of pneumonia in the previous year, and history of severe exacerbation in the previous year

*MACCE included death from any cause, myocardial infarction, revascularization, and ischemic stroke

In terms of cardiovascular outcomes, successfully quitting smoking was associated with a reduced risk of MACCE compared with continued cigarette smoking (aHR = 0.85; 95% CI = 0.79, 0.93). Switching to e-cigarettes was also associated with a lower risk of MACCE (aHR = 0.80; 95% CI = 0.66, 0.97). When individual cardiovascular components were examined, successful quitting was associated with significantly lower risks of myocardial infarction, revascularization, and ischemic stroke. Among participants who switched to e-cigarettes, point estimates suggested lower risks of myocardial infarction (aHR = 0.52; 95% CI = 0.26, 1.06) and revascularization (aHR = 0.76; 95% CI = 0.53, 1.10), although these associations did not reach statistical significance. Similar trends were observed in competing risk models (Table 2). The risk of death (aHR = 0.82; 95% CI = 0.63, 1.06) was also lower in e-cigarette use, but it was not statistically significant. Compared with continued cigarette smoking group, completed switching to e-cigarette group had a trend toward risk reduction in MACCE (aHR = 0.74; 95% CI = 0.52, 1.04) (Table 3).

In sensitivity analysis, restricting the cohort to participants whose Exam 2 occurred within 12 months of COPD diagnosis, the results were consistent (Supplementary Table 2). When analyses were repeated using models adjusted only for baseline covariates, the associations between smoking behavior after COPD diagnosis and study outcomes were consistent with the main results (Supplementary Table 3). Furthermore, in the propensity score matched cohort, results were concordant

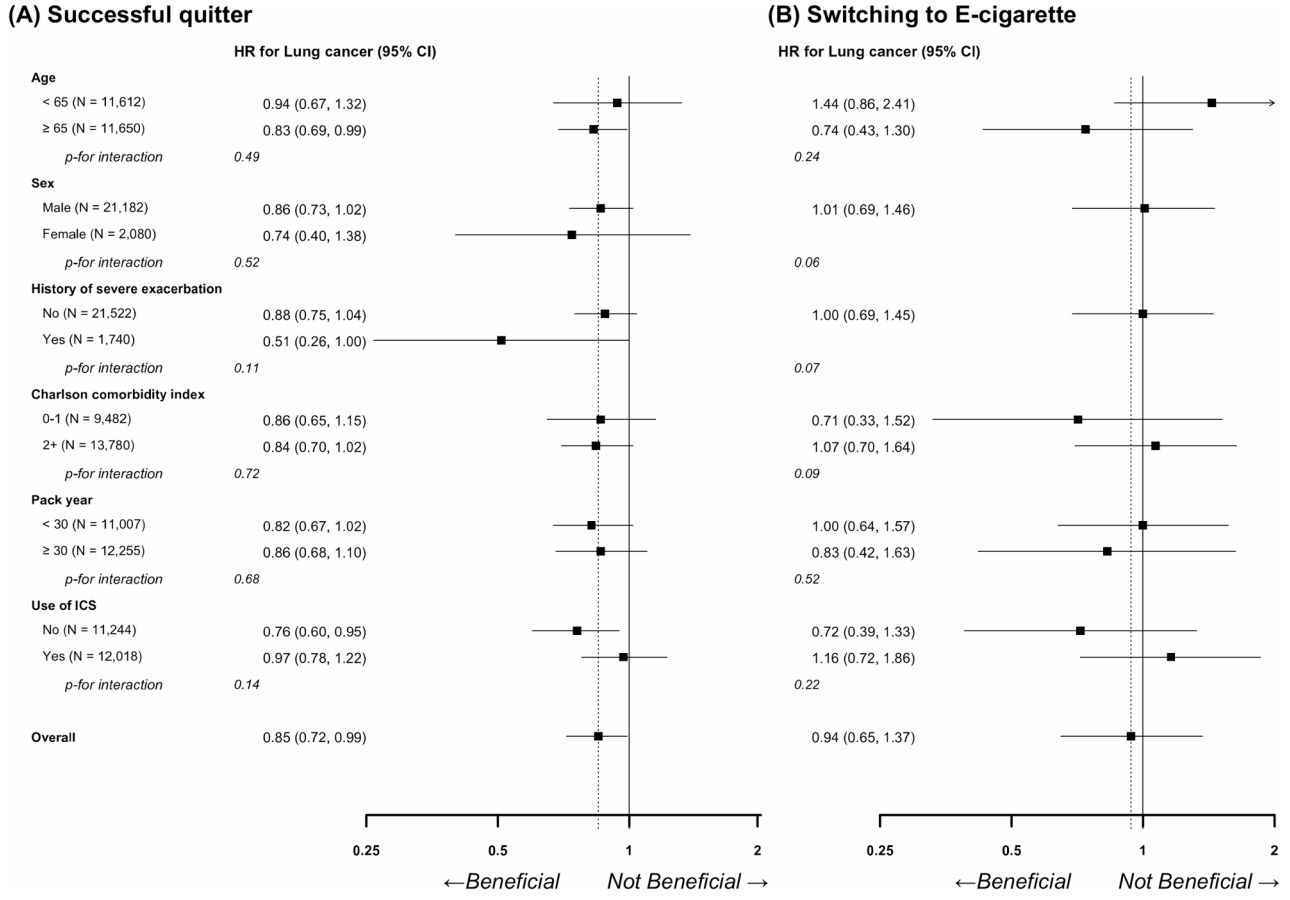


Fig. 2 Subgroup analysis of adjusted hazard ratios for lung cancer according to smoking behavior changes after COPD diagnosis. Panel (**B**) follows the same subgroup definitions and analytical approach as panel (**A**). HRs were not estimable for female users and those with a history of severe exacerbation in the e-cigarette switching group due to zero lung cancer events. HR = hazard ratio; CI = confidence interval; ICS = inhaled corticosteroid; e-cigarette = electronic cigarette

with those of the main multivariable-adjusted models (Supplementary Table 4). When restricted to individuals who maintained their reported smoking category at subsequent follow-up examinations showed MACCE still significantly lower than continuous smoker, and other outcome also directionally consistent associations, although statistical power was limited (Supplementary Table 5).

Discussion

In this large nationwide cohort of Korean patients newly diagnosed with COPD who were current smokers at the time of diagnosis, complete smoking cessation following diagnosis was associated with significantly lower risks of lung cancer, COPD exacerbation, MACCE, and all-cause mortality. In contrast, switching to e-cigarettes did not yield significant reductions in lung cancer incidence and COPD exacerbations, although it was associated with a lower risk of MACCE compared with continued combustible cigarette smoking. While point estimates for exclusive e-cigarette users were generally favorable, the limited statistical power in this subgroup precluded definitive conclusions. Ultimately, our findings reinforce that complete smoking cessation remains the most effective strategy for optimizing long-term clinical outcomes in patients with COPD.

Our findings are consistent with established evidence that complete smoking cessation reduces the risk of COPD exacerbations [23], lung cancer development [24], and adverse cardiovascular outcomes [25] in patients with COPD. Beyond these proven benefits, our study was designed to address the critical question of whether e-cigarettes serve as effective smoking cessation or harm-reduction tools specifically for patients with COPD, a population at exceptionally high risk for smoking-related complications. Many e-cigarette retailers, and advocates have promoted e-cigarettes as effective aids for ceasing smoking [26], leading many individuals to adopt them a less harmful alternative to combustible cigarettes [5]. However, mounting evidence suggests that the adverse health effects of e-cigarette use are substantial [7, 9, 11, 12, 27]. Consistent with these concerns,

our results demonstrated that switching to e-cigarettes provided minimal benefits in terms of all-cause mortality, lung cancer risk, and COPD exacerbations compared with continued combustible cigarette use. These findings address the knowledge gap in the literature regarding the clinical outcomes of e-cigarette switching, particularly among patients with pre-existing chronic diseases [12]. While a previous small-scale prospective study involving 39 patients suggested potential benefits [14], our study significantly expands upon those findings by utilizing a large, nationally representative cohort and evaluating clinically relevant hard endpoints, such as lung cancer incidence and COPD exacerbations. The lack of significant risk reduction for these outcomes among e-cigarette switchers underscores the uncertainty surrounding their long-term safety in the COPD population, emphasizing that complete smoking cessation remains the primary mainstay for mitigating future harm from cigarette exposure.

In contrast to respiratory outcomes, cardiovascular outcomes, such as MACCE, showed improvement among those who switched to e-cigarettes. According to a recent meta-analysis, patients with COPD face a particularly high and dynamic cardiovascular risk, which escalates sharply following acute exacerbations and remains elevated for several months [28]. This heightened vulnerability may render cardiovascular outcomes more responsive even to partial reductions in combustible cigarette exposure. Our findings are consistent with a recent large population-based cohort study [13] showing that smokers who switched to e-cigarettes after percutaneous coronary intervention experienced an 18% reduction in major adverse cardiovascular events compared to continued smokers. In the present study, the composite outcome (MACCE) reached statistical significance, while the individual components exhibited only a trend toward decreasing adverse events. The observed divergence between respiratory and cardiovascular outcomes may be attributed to the distinct pathophysiological responses of each system to cigarette exposure. Cardiovascular benefits can often be realized through rapid improvements in endothelial function and the reversal of acute inflammatory responses following smoking cessation [29]. In contrast, respiratory damage in COPD involves largely irreversible structural changes that may require total cessation for clinically meaningful improvement. Furthermore, the direct exposure of lung tissues to e-cigarette aerosols may perpetuate localized airway inflammation and oxidative stress [30, 31]. This localized damage likely limits the respiratory benefits that might otherwise be expected from the cardiovascular improvements observed in this population, where the effects tend to be more systemic.

Our study had several important limitations. First, the COPD diagnosis was determined using health insurance claims data, relying on a combination of disease codes and COPD medication prescriptions. Because spirometry results were not available, there is a possibility of misclassification inherent to this approach. Nevertheless, this definition has been examined and validated in several previous studies [17–19]. Second, as this study relied on a large-scale national database, we were unable to distinguish between specific types of e-cigarette products used by participants. Given the significant heterogeneity in device formulations, delivery systems, and nicotine concentrations, such lack of granular data may have masked potential differences in outcomes related to specific product characteristics. Third, exposure misclassification is an inherent concern, particularly among dual users. However, despite the relatively small sample of exclusive e-cigarette users, sensitivity analyses separating exclusive use from dual use yielded directionally consistent associations. Although smoking behaviors can fluctuate, making it challenging to capture the long-term stability of switching, a substantial reduction in combustible cigarette consumption was directly observed among those classified as e-cigarette users. Consequently, any residual misclassification is likely to have been non-differential, which would typically bias outcomes toward the null rather than generate spurious protective associations. Finally, given the retrospective nature of this study, unmeasured confounders such as environmental exposures (e.g., air pollution), occupational risk factors, or adherence to inhaler therapy may have influenced the observed associations.

Conclusions

In patients with COPD, complete smoking cessation was associated with significantly reduced risks of lung cancer, all-cause mortality, and COPD exacerbations. While switching to e-cigarettes was associated with a lower risk of MACCE compared with continued cigarette smoking, it did not yield comparable respiratory benefits. These findings are associative and do not necessarily imply that switching to e-cigarettes is unsafe, as no significant increase in lung cancer or COPD exacerbation risk was observed relative to continued cigarette smoking. However, given the limited statistical power among exclusive e-cigarette users and non–time-updated exposure assessments, further studies with larger cohorts and longitudinal monitoring are warranted.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12931-026-03545-1.

Supplementary Material 1.

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None.

Authors' contributions
TK : Writing the original draft, HK & DK : formal analysis and Methodology, SHS, SC, EJ, & LC: Validation. HYP : Writing, review, editing, supervision, and project administration. All the authors discussed the results and approved the final version of the manuscript.

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Data availability
The data are available from the Korean National Health Insurance Sharing Service (NHISS; https://nhiss.nhis.or.kr/) database, which is open to researchers on request with approval by the Institutional Review Board.

Declarations

Ethics approval and consent to participate
This study was approved by the Institutional Review Board of the Samsung Medical Center (IRB No. SMC 2024-03-120). The requirement for informed consent was waived due to the use of de-identified administrative data. All study procedures were conducted in accordance with relevant guidelines and regulations, including the Declaration of Helsinki.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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