



Increased risk of coronary heart disease and stroke in lung cancer survivors: A Korean nationwide study of 20,458 patients

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ABSTRACT

Objectives: With advances in lung cancer treatments, the number of lung cancer survivors has increased. As cardiovascular diseases (CVD) are some of the major causes of non-cancer deaths, CVD management is an integral part of cancer survivorship care. However, there is sparsity of data on cardiovascular risk in lung cancer survivors who underwent lung cancer surgery. We aimed to compare the incidence of CVD between lung cancer survivors and the general non-cancer population.

Materials and methods: Using the Korean National Health Insurance Service Database, we selected 20,458 patients who underwent surgery for lung cancer between 2007 and 2013. Study outcome variables were coronary heart disease (CHD), myocardial infarction (MI), ischemic stroke (IS), and death. Patients were followed until 2016.

Results: A total of 20,458 lung cancer patients undergoing lung cancer surgery were compared to 27,321 non-cancer control subjects. Lung cancer survivors showed a greater risk for all cardiovascular (CV) events (adjusted hazard ratio [aHR] = 1.27, 95% confidence interval [CI]: 1.19–1.36), CHD (aHR = 1.26, 95% CI: 1.16–1.36), and IS (aHR = 1.22, 95% CI: 1.07–1.39). Chemotherapy and radiotherapy were associated with an increased risk of CV events, CHD, and MI. Lung cancer survivors who were CV event-free for one year, and up to three years, were still at a higher risk for all CV events compared to the non-cancer control population.

Conclusions: Lung cancer survivors showed an increased risk of CHD and IS compared with the general non-cancer population. Therefore, paying careful attention to cardiovascular risk in lung cancer survivors is suggested, especially for those who receive chemotherapy and/or radiotherapy, in order to ensure both early and long-term survivorship.

1. Introduction

Lung cancer is currently one of the most common cancers worldwide, with increasing rates of diagnoses. There are 2,093,876 annual incident cases of lung cancer worldwide [1], with 234,030 in the US [2] and 25,780 in Korea [3]. With the advancement of lung cancer treatments, the survivorship of lung cancer patients has improved. Five-year survival rates for localized lung cancer has increased from 49% [4] to

56% [2] in the US, with rates increasing from 16.5% to 27.1% for all lung cancer stages in Korea [5]. As a result, the number of lung cancer survivors has increased substantially, with an estimated 526,510 lung cancer survivors in the US as of January 1, 2016 [6].

With a growing number of lung cancer survivors, managing comorbidities has become increasingly important for this population. Cardiovascular disease (CVD) is one of the major causes of non-cancer deaths [7], especially in long-term survivors, and should be an integral

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part of cancer survivorship care.

Although several studies have investigated cardiovascular (CV) risk in lung cancer survivors [8–16], they have primarily focused on the CV risk of lung cancer patients regardless of stage or operability [9–15], and did not provide any treatment information [8–10,13,9–16], did not conduct an analyses based on the follow-up period [8,11,12], and/or had limited CV events [12,13]. Additionally, most studies were based on data from western countries [8–14,16]. Furthermore, a recent Dutch study [11] defined CVD broadly, and therefore lacked any discussion on major arterial thromboembolic events, including coronary heart disease (CHD), myocardial infarction (MI), and ischemic stroke (IS).

In this Korean nationwide study, we investigated CHD, MI, and IS incidence rates among lung cancer patients who underwent surgery compared to a general population of non-cancer control individuals.

2. Materials and methods

2.1. Data source: Korean National Health Insurance Service (KNHIS) database

Korean National Health Insurance Service (KNHIS) is a single government payer providing universal public health insurance to almost the whole Korean population (approximately 97% of the population). Individuals in the lowest income level bracket (approximately 3% of the population) are covered by the Medical Aid program, which is funded by general taxes. KNHIS manages the qualification of beneficiaries for both programs, and therefore has demographic data, such as age, sex, residential area, and income status. In Korea, an individual's insurance contribution is determined by their monthly income level, and not by their health risk, and can therefore be used as a proxy for economic status.

Medical service providers in Korea are mostly private and are reimbursed for their medical services mainly on a fee-for-service basis. Therefore, the KNHIS contains all the data necessary for reimbursement, including disease codes (based on the International Classification of Disease [ICD]-10), outpatient clinic visits and hospital admission, a detailed list of diagnostic tests, procedures and other medical treatments performed, prescription of medications, and billed costs.

The KNHIS provides a free biennial health screening program to all Korean people over 40 years of age and for those who are employee regardless of age [17]. This program aims to detect cardiovascular risk factors, including hypertension, diabetes, and dyslipidemia, for subsequent educational counseling or treatment referral plans. The program includes a questionnaire on medical history and health behavior (e.g., smoking, alcohol consumptions, etc.), anthropometric measurements (e.g., blood pressure, body mass index [BMI], etc.), and laboratory tests (e.g., fasting blood glucose, lipid profile, etc.).

The KNHIS database is an accurate source of real-world data, and has been widely used in numerous epidemiological and health services-related research studies [18]. Its detailed profile and configuration have been previously described [19,20]. The informed consent of each study subject was waived as the study was based on routinely collected insurance claims data.

2.2. Study population

In this retrospective administrative data study, we selected a total of 33,036 patients who underwent surgery for lung cancer treatment (ICD-10 code C34) from January 1, 2007 to December 31, 2013. We excluded patients under the following criteria: 1) less than 19 years old (N = 39); 2) diagnosed previously with other cancers (C00-C97 except C34, N = 5432) before lung cancer diagnosis; 3) experienced CHD (I20-I25) or stroke (I63) before lung cancer surgery (N = 4223); and 4) survived < 1 year from the date of surgery (N = 2884). Finally, 20,458 lung cancer patients were included in the analyses. Among those, 13,338 patients participated in the national health screening program

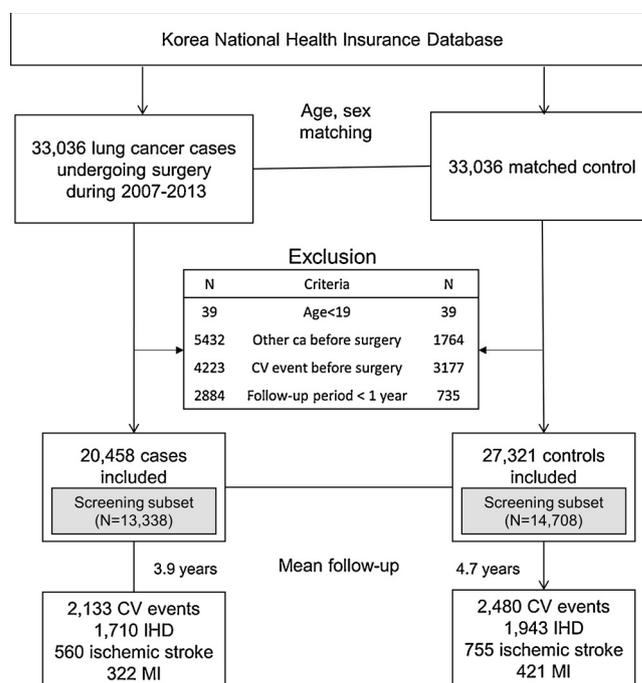


Fig. 1. Study participants.

and had information on smoking and BMI and therefore comprised the screening subset population. The details of chemotherapy and radiotherapy regimens could not be acquired from the KNHIS database.

For selection of the control group, we used 1:1 age, sex-matching. Matching were serially performed year-by-year so that patients who received surgery during a specific year were matched to control subjects who were alive in the same year based on age and sex. Control subjects were assigned an index date that corresponded to the date of lung cancer surgery for their matched lung cancer survivor. Identical exclusion criteria were applied to control subjects: 1) < 19 years (N = 39); 2) previous cancer history (N = 1764); 3) previous CHD or stroke (N = 3177); and 4) survival < 1 year from index date (N = 735). The study population selection scheme is illustrated in Fig. 1.

2.3. Study outcomes and follow-up

The endpoints of the study were newly diagnosed CHD, MI, stroke, or death. CHD was defined as the recording of ICD-10 codes I20-I25 during; MI was defined as the recording of ICD-10 codes I21 or I22 during hospitalization. Stroke was defined as the recording of ICD-10 codes I63 or I64 during hospitalization with claims for brain magnetic resonance imaging or brain CT scan. Although it was difficult to clearly define the subtype (ischemic vs. hemorrhagic) of stroke, we attempted to exclude cerebral hemorrhaging. Subjects without CHD or stroke during their follow-up periods were considered to have completed the study at the date of their death or at the end of the follow-up period, whichever came first. The study population was followed from baseline to the date of death or cardiovascular events, or until 31 December 2016, whichever came first.

2.4. Covariates

The following conditions were included: hypertension (I10-I11 and antihypertensive medication), diabetes mellitus (E10-E14 and anti-diabetic medication), dyslipidemia (E78 and lipid-lowering agent), and chronic obstructive pulmonary disease (COPD, J40-J47). Income level was categorized into quartiles based on individual insurance contribution; the medical aid population (~3% of Korean population) were merged with the lowest income quartile group for the analyses. Place of

residence was categorized into metropolitan, urban, and rural areas based on the level of urbanization. In the screening subset group, information on smoking (current, past, never) and BMI (categorized into < 18.5, 18.5–23, 23–25, 25–30, and ≥ 30 according to the Asian criteria for obesity) were also included.

2.5. Statistical analyses

Descriptive statistics were used to determine the basic characteristics of lung cancer survivors and their matched controls. Cox proportional-hazards regression analysis was used to determine the relative risk for each study outcome. The multivariate model was adjusted for age, sex, income, place of residence, hypertension, diabetes, dyslipidemia, COPD, and treatment. The screening subset group was further adjusted for smoking status and BMI.

As lung cancer patients are more likely to die of lung cancer than their matched controls, and lung cancer deaths can compete with incidences of CHD and stroke, we performed sensitivity analyses by considering excess mortality in lung cancer survivors. A semi-parametric proportional hazards regression model by Fine and Gray was used in the competing risk regression analyses [21]. Risk was presented as a subdistribution hazard ratio (SHR) and 95% confidence interval (CI).

To examine the effect of chemo- and radiotherapy on the risk of CHD and stroke among lung cancer survivors, analyses were made based on treatment types: 1) surgery only; 2) surgery + chemotherapy; 3) surgery + radiotherapy; and 4) surgery + chemotherapy + radiotherapy. To investigate the relative risk based on the CV event-free survival period, analyses were repeated with the 3-year CV-event free survivors, and the 5-year CV-event free survivors. All statistical analyses were performed by SAS version 9.1 (SAS institute, Cary, NC), with P -values < 0.05 considered statistically significant.

3. Results

3.1. Characteristics of the study population

A total of 20,458 lung cancer patients undergoing lung cancer surgery were compared to 27,321 age- and sex-matched non-cancer control subjects. Lung cancer patients tended to be younger than control subjects (60.9 vs. 61.2 years, $P < 0.001$) and were slightly more likely to be female (37.5% vs. 36.5%, $P = 0.039$). Lung cancer patients had a higher prevalence of hypertension (38.2% vs. 32.9%, $P < 0.001$), diabetes mellitus (15.0% vs. 12.3%, $P < 0.001$), dyslipidemia (19.6% vs. 15.5%, $P < 0.001$), and COPD (54.4% vs. 9.0%, $P < 0.001$) than matched control subjects at baseline. Among lung cancer patients, 84.1% received a lobectomy, 17.4% received wedge resection, 39.2% underwent chemotherapy, and 15.1% received radiotherapy.

The screening subset group included 13,338 lung cancer patients and 14,708 age- and sex-matched non-cancer control subjects. Lung cancer patients reported both a lower current smoking rate (52.7% vs. 60.1%, $P < 0.001$), and lower BMI ($P < 0.001$) (Table 1).

3.2. CVD risk in lung cancer patients compared to non-cancer controls

The mean follow-up period after surviving 1 year were 3.93 and 4.69 years for the lung cancer patients and for the non-cancer control subjects, respectively. Compared to the control subjects, conventional Cox proportional-hazards regression analyses showed a greater risk for all CV events (adjusted hazard ratio [aHR] = 1.27, 95% CI: 1.19–1.36), CHD (aHR = 1.26, 95% CI: 1.16–1.36), and IS (aHR = 1.22, 95% CI: 1.07–1.39) in lung cancer survivors. Analyses of the screening subset group also showed similar results for all CV events, CHD, and IS. In the competing risk analyses, lung cancer survivors were shown to be at similar risk for all CV events (adjusted SHR [aSHR] = 1.05, 95% CI: 0.99–1.13), CHD (aSHR = 1.03, 95% CI: 0.95–1.11), IS (aSHR = 1.01,

95% CI: 0.89–1.15), and MI (aSHR = 0.87, 95% CI: 0.73–1.04) in comparison to non-cancer control subjects. Incidence of the probability of all CV event, CHD, and stroke in lung cancer survivors and control group is illustrated in Fig. 2. Analyses of the screening subset group also showed similar non-significant results (Table 2).

3.3. CVD risk in lung cancer patients by treatment modalities

Among lung cancer patients, both chemotherapy (aHR = 1.29, 95% CI: 1.17–1.43) and radiotherapy (aHR = 1.62, 95% CI: 1.32–1.99) were associated with an increased risk of CV events. Receiving both treatments were associated with an even higher risk of developing CV events (aHR = 2.06, 95% CI: 1.79–2.35). Similar patterns were observed for CHD and MI. For IS, only those who received radiotherapy after surgery were not at a higher risk (aHR = 1.43, 95% CI: 0.94–2.17) (Table 3).

3.4. CVD risk in lung cancer patients by CV event-free survival period

Lung cancer survivors who were CV event-free for one year were later at higher risk for developing CV events (aHR = 1.21, 95% CI: 1.12–1.30), CHD (aHR = 1.19, 95% CI: 1.09–1.29), and IS (aHR = 1.11, 95% CI: 1.05–1.41) compared to non-cancer control subjects. Lung cancer survivors who were CV event free for three years also showed a higher risk for developing CV events (aHR = 1.16, 95% CI: 1.04–1.29). However, lung cancer survivors who were CV event-free for five years exhibited a similar risk for developing CV events as non-cancer control subjects (aHR = 1.03, 95% CI: 0.86–1.23) (Table 4).

4. Discussion

To our knowledge, this is the first nationwide study to directly investigate the relative risk of CHD and stroke incidences among lung cancer survivors, who underwent surgical resection, compared to a general non-cancer control population. Major strengths of our study include the use of national claims data, which enabled a larger sample size, as well as the inclusion of age- and sex-matched non-cancer controls, with low attrition rates. Moreover, adjusting for various socio-demographic and major cardiovascular risk factors were possible through linkages with health screening data.

We found that lung cancer survivors undergoing surgery who survived at least one year were at a higher risk of CHD and IS compared to the general control population. Several studies showed that lung cancer patients did not have an increased risk of CHD or IS compared with the general population [12–14]. However, many other studies reported increased CV risk among lung cancer survivors [8–11,15,16], even among those with early stage lung cancer [8], although the pre-operative settings of the study population were not fully examined in these studies. Acquired thrombophilia due to cancer and perioperative chemo- and radiotherapy might play a crucial role in increasing the risk of CHD and IS [22–24]. An American study, based on the data of residents in southern California [8], found that 1195 2-year survivors of lung cancer had a significantly higher risk of CVD, including IHD, stroke, and heart failure, when compared with age-, sex-, and place of residence-matched non-cancer controls. This study also conducted exploratory analyses based on cancer stage at diagnosis and demonstrated an incremental risk with each stage among survivors with advanced stage lung cancer. When competing risks were considered in the statistical analyses, the SHR was smaller than the HR obtained by a conventional Cox regression model. This could happen when both the cause-specific risk of event of interest (i.e., CV event in this study) and the cause-specific risk of competing event (i.e., death from other causes, especially lung cancer) are greater in the lung cancer survivor group than in the comparison group [25]. The sensitivity analyses also confirmed that lung cancer survivors are at least on the same level of CV risk as the general population, and emphasizes the need for proper CV risk management during their survivorship period.

Table 1
Baseline characteristics of study participants.

	All lung cancer patients		P-value	Screening subgroup		P-value
	General population	Lung cancer patients		General population	Lung cancer patients	
N	27,321	20,458		14,708	13,338	
Age			< 0.001			< 0.001
mean, SD (years)	61.2 ± 10.1	60.9 ± 10.1		61.5 ± 9.3	61.3 ± 9.5	
19-40 years	696 (2.6)	528 (2.6)		215 (1.5)	230 (1.7)	
40-65 years	15,355 (56.2)	11,800 (57.7)		8489 (57.7)	7813 (58.6)	
65-75 years	9345 (34.2)	6693 (32.7)		5139 (34.9)	4409 (33.1)	
> 75 years	1925 (7.1)	1437 (7.0)		865 (5.9)	886 (6.6)	
Sex			0.039			0.006
Male	17,339 (63.5)	12,795 (62.5)		9461 (64.3)	8368 (62.7)	
Female	9982 (36.5)	7663 (37.5)		5247 (35.7)	4970 (37.3)	
Income status			< 0.001			< 0.001
Rank 16-20 (highest)	7363 (27.0)	6452 (31.5)		4091 (27.8)	4079 (30.6)	
Rank 11-15	6387 (23.4)	4952 (24.2)		3585 (24.4)	3357 (25.2)	
Rank 6-10	5732 (21.0)	4062 (19.9)		3231 (22.0)	2829 (21.2)	
Rank 1-5 (lowest) + Medical aid	7839 (28.7)	4992 (24.4)		3801 (25.8)	3073 (23.0)	
Place of residence			< 0.001			0.002
Metropolitan	16,510 (60.4)	12,667 (61.9)		8742 (59.4)	8131 (61.0)	
City	7404 (27.1)	5433 (26.6)		4008 (27.3)	3606 (27.0)	
Rural	3407 (12.5)	2358 (11.5)		1958 (13.3)	1601 (12.0)	
Comorbidities						< 0.001
Hypertension	8987 (32.9)	7813 (38.2)	< 0.001	5116 (34.8)	5108 (38.3)	< 0.001
Diabetes Mellitus	3357 (12.3)	3067 (15.0)	< 0.001	1870 (12.7)	1924 (14.4)	< 0.001
Dyslipidemia	4247 (15.5)	4007 (19.6)	< 0.001	2582 (17.6)	2658 (19.9)	< 0.001
COPD	2453 (9.0)	11,118 (54.4)	< 0.001	1359 (9.2)	7216 (54.1)	< 0.001
Treatment						
Surgery						
Wedge resection		3560 (17.4)			2293 (17.2)	
Segmentectomy		523 (2.6)			338 (2.5)	
Lobectomy		17,200 (84.1)			11,375 (85.3)	
Pneumonectomy		886 (4.3)			496 (3.7)	
Chemotherapy		8015 (39.2)			5168 (38.7)	
Radiotherapy		3081 (15.1)			1950 (14.6)	
Treatment, combination						
Surgery only		11,742 (57.4)			7734 (58.0)	
Surgery + CT		5635 (27.5)			3654 (27.4)	
Surgery + RT		701 (3.4)			436 (3.3)	
Surgery + CT + RT		2380 (11.6)			1514 (11.4)	
Smoking						< 0.001
Current				8842 (60.1)	7028 (52.7)	
Past				2773 (18.9)	2526 (18.9)	
Never				3093 (21.0)	3784 (28.4)	
Body mass index						< 0.001
< 18.5				390 (2.7)	421 (3.2)	
18.5–23				5152 (35.0)	5271 (39.5)	
23–25				4081 (27.8)	3654 (27.4)	
25–30				4652 (31.6)	3701 (27.8)	
≥ 30				433 (2.9)	291 (2.2)	

Values are n (%).

SD: Standard deviation; COPD: chronic obstructive pulmonary disease; RT: radiotherapy; CT: chemotherapy.

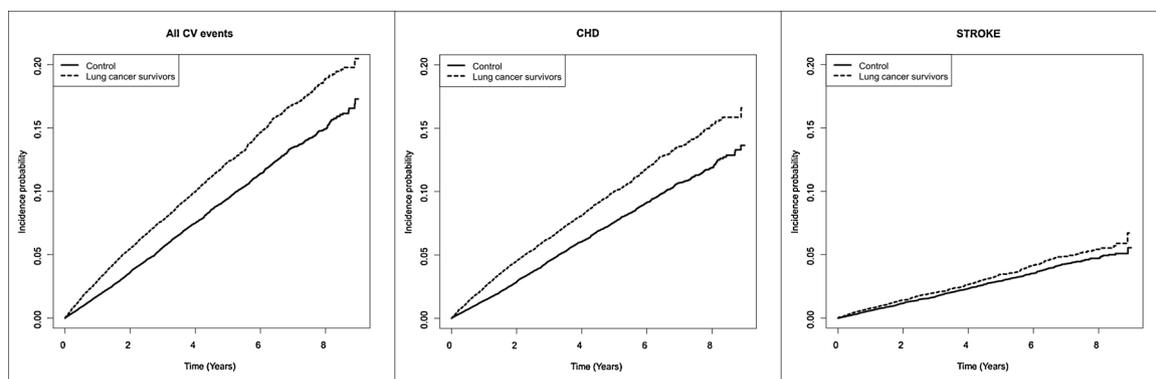


Fig. 2. Incidence of the probability of all cardiovascular(CV) event, coronary heart disease (CHD), and stroke in lung cancer survivors and control group.

Table 2
Risk of cardiovascular events in lung cancer survivors and the general non-cancer control population comparison group: Cox-regression and competing risk analyses.

	N	N. event	Rate	Conventional Cox regression		Competing risk analysis	
				Crude HR (95% CI)	Adjusted HR (95% CI)	Crude SHR (95% CI)	Adjusted SHR (95% CI)
All subjects							
All CV events							
Comparison group	27,321	2,480	19.3	1 (Ref.)	1 (Ref.)	1 (ref.)	1 (ref.)
Lung cancer survivors	20,458	2,133	26.5	1.38 (1.30-1.46)	1.27 (1.19-1.36)	1.15 (1.09-1.22)	1.05 (0.99-1.13)
CHD							
Comparison group	27,321	1,943	15.2	1 (Ref.)	1 (Ref.)	1 (ref.)	1 (ref.)
Lung cancer survivors	20,458	1,710	21.3	1.41 (1.32-1.50)	1.26 (1.16-1.36)	1.16 (1.09-1.24)	1.03 (0.95-1.11)
Ischemic stroke							
Comparison group	27,321	755	5.9	1 (Ref.)	1 (Ref.)	1 (ref.)	1 (ref.)
Lung cancer survivors	20,458	560	7.0	1.19 (1.06-1.32)	1.22 (1.07-1.39)	0.99 (0.89-1.10)	1.01 (0.89-1.15)
MI							
Comparison group	27,321	421	3.3	1 (Ref.)	1 (Ref.)	1 (ref.)	1 (ref.)
Lung cancer survivors	20,458	322	4.0	1.22 (1.06-1.41)	1.14 (0.96-1.35)	0.98 (0.85-1.13)	0.87 (0.73-1.04)
Screening subgroup							
All CV events							
Comparison group	14,708	1,239	18.6	1 (Ref.)	1 (Ref.)	1 (ref.)	1 (ref.)
Lung cancer survivors	13,338	1,298	25.4	1.37 (1.27-1.48)	1.24 (1.13-1.35)	1.18 (1.09-1.28)	1.05 (0.96-1.15)
CHD							
Comparison group	14,708	992	14.9	1 (Ref.)	1 (Ref.)	1 (ref.)	1 (ref.)
Lung cancer survivors	13,338	1,019	19.9	1.34 (1.23-1.46)	1.19 (1.08-1.32)	1.15 (1.06-1.26)	1.02 (0.92-1.13)
Ischemic stroke							
Comparison group	14,708	339	5.1	1 (Ref.)	1 (Ref.)	1 (ref.)	1 (ref.)
Lung cancer survivors	13,338	366	7.2	1.41 (1.22-1.64)	1.35 (1.14-1.61)	1.20 (1.04-1.39)	1.12 (0.94-1.34)
MI							
Comparison group	14,708	190	2.9	1 (Ref.)	1 (Ref.)	1 (ref.)	1 (ref.)
Lung cancer survivors	13,338	194	3.8	1.34 (1.09-1.63)	1.10 (0.87-1.39)	1.13 (0.93-1.38)	0.91 (0.71-1.17)

CI: Confidence Interval; CV: cardiovascular; CHD: coronary heart disease; MI: myocardial infarction.
Adjusted for age, sex, income, place of residence, hypertension, diabetes, dyslipidemia, and chronic obstructive pulmonary disease for all subjects; and smoking and body mass index for screening subgroup.

Table 3
Cardiovascular risk among lung cancer survivors by lung cancer treatment group.

By treatment group	N	Event	Rate per 1000	Crude HR (95% CI)	Adjusted HR (95% CI)
All CV events					
Surgery only	11,742	1,139	23.1	1 (Ref.)	1 (Ref.)
Surgery + CT	5635	620	28.6	1.24 (1.12-1.37)	1.29 (1.17-1.43)
Surgery + RT	701	102	41.7	1.80 (1.47-2.20)	1.62 (1.32-1.99)
Surgery + CT + RT	2380	272	39.6	1.70 (1.49-1.94)	2.06 (1.79-2.35)
CHD					
Surgery only	11,742	926	18.7	1 (Ref.)	1 (Ref.)
Surgery + CT	5635	488	22.5	1.20 (1.07-1.34)	1.25 (1.12-1.40)
Surgery + RT	701	83	33.9	1.80 (1.44-2.26)	1.63 (1.30-2.04)
Surgery + CT + RT	2380	213	31.0	1.63 (1.40-1.89)	1.97 (1.69-2.29)
Ischemic stroke					
Surgery only	11,742	298	6.0	1 (Ref.)	1 (Ref.)
Surgery + CT	5635	168	7.8	1.28 (1.06-1.55)	1.35 (1.11-1.63)
Surgery + RT	701	24	9.8	1.61 (1.06-2.44)	1.43 (0.94-2.17)
Surgery + CT + RT	2380	70	10.2	1.68 (1.29-2.18)	2.12 (1.62-2.77)
MI					
Surgery only	11,742	166	3.4	1 (Ref.)	1 (Ref.)
Surgery + CT	5635	103	4.8	1.41(1.10-1.80)	1.51 (1.18-1.94)
Surgery + RT	701	17	6.9	2.05 (1.25-3.38)	1.82 (1.10-3.01)
Surgery + CT + RT	2380	36	5.2	1.53 (1.07-2.19)	1.96 (1.35-2.83)

CI: Confidence Interval; CV: cardiovascular; CHD: coronary heart disease; MI: myocardial infarction.
Adjusted for age, sex, income, place of residence, hypertension, diabetes, dyslipidemia, and chronic obstructive pulmonary disease.

In the current study, among lung cancer survivors, those who received radiotherapy or chemotherapy were at a higher risk of CHD and IS than those who received surgery only. Several studies demonstrated that chemotherapy and thoracic radiotherapy were associated with an increased risk of CV events [23,24,26–33]. More specifically, this is also consistent with a previous study [8] in which stage III/IV lung cancer patients were at a higher risk for CV events (incidence rate ratio [IRR] = 2.01, 95% CI: 1.56–2.60) when compared to the matched general population comparison cohort, than those with stage I/II cancer

(IRR = 1.39, 95% CI: 1.10–1.75). It is well known that radiotherapy can increase the probability of circulatory diseases, such as CHD and cerebrovascular diseases [23]. Although there are a limited number of studies showing the cardiac effect of radiotherapy on lung cancer patients due to their limited life expectancy, several studies have demonstrated cardiac toxicity and increased risk of IS after radiotherapy for non-small cell lung cancer [26–29]. Previous studies suggest that radiotherapy could cause cardiac toxicity by inducing early microvascular changes and the development of late atherosclerosis in major

Table 4

Risk of cardiovascular events in lung cancer survivors and the general non-cancer population comparison group by cardiovascular event-free survival period.

	after 1 year				after 3 years				after 5 years			
	N	N. event	Rate	adjusted HR (95% CI)	N	N. event	Rate	adjusted HR (95% CI)	N	N. event	Rate	adjusted HR (95% CI)
All subjects												
All CV events												
Comparison	26,644	2031	15.9	1 (Ref.)	20,426	1105	9.8	1 (Ref.)	11,376	447	5.8	1 (Ref.)
LC survivors	18,439	1544	19.5	1.21 (1.12-1.30)	12,511	734	11.1	1.16 (1.04-1.29)	6111	266	6.5	1.03 (0.86-1.23)
CHD												
Comparison	26,644	1589	12.4	1 (Ref.)	20,426	855	7.6	1 (Ref.)	11,376	338	4.4	1 (Ref.)
LC survivors	18,439	1231	15.5	1.19 (1.09-1.29)	12,511	572	8.6	1.13 (1.00-1.28)	6111	204	5.0	1.01 (0.82-1.24)
Ischemic stroke												
Comparison	26,644	597	4.7	1 (Ref.)	20,426	329	2.9	1 (Ref.)	11,376	136	1.8	1 (Ref.)
LC survivors	18,439	406	5.1	1.21 (1.05-1.41)	12,511	206	3.1	1.21 (0.99-1.48)	6111	75	1.8	1.07 (0.77-1.49)
MI												
Comparison	26,644	336	2.6	1 (Ref.)	20,426	194	1.7	1 (Ref.)	11,376	66	0.9	1 (Ref.)
LC survivors	18,439	226	2.8	1.11 (0.91-1.36)	12,511	105	1.6	1.00 (0.75-1.31)	6111	38	0.9	1.03 (0.64-1.64)
Subgroup												
All CV events												
Comparison	14,399	1018	15.3	1 (Ref.)	10,862	530	9.2	1 (Ref.)	5470	212	5.8	1 (Ref.)
LC survivors	12,107	943	18.7	1.17 (1.05-1.29)	8079	417	10.0	1.09 (0.94-1.27)	3646	139	5.8	0.91 (0.71-1.18)
CHD												
Comparison	14,399	815	12.3	1 (Ref.)	10,862	414	7.1	1 (Ref.)	5,470	164	4.5	1 (Ref.)
LC survivors	12,107	735	14.5	1.11 (0.99-1.25)	8079	316	7.6	1.05 (0.88-1.25)	3646	108	4.5	0.93 (0.69-1.24)
Ischemic stroke												
Comparison	14,399	271	4.1	1 (Ref.)	10,862	151	2.6	1 (Ref.)	5470	60	1.6	1 (Ref.)
LC survivors	12,107	267	5.3	1.31 (1.07-1.60)	8079	131	3.2	1.24 (0.94-1.63)	3646	37	1.5	0.90 (0.55-1.46)
MI												
Comparison	14,399	154	2.3	1 (Ref.)	10,862	88	1.5	1 (Ref.)	5470	34	0.9	1 (Ref.)
LC survivors	12,107	138	2.7	1.06 (0.81-1.40)	8079	59	1.4	0.88 (0.59-1.29)	3646	18	0.7	0.72 (0.36-1.43)

CI: Confidence Interval; CV: cardiovascular; Comparison: Comparison group; LC survivors: Lung Cancer Survivors; HR: hazard ratio; CHD: coronary heart disease; MI: myocardial infarction.

Adjusted for age, sex, income, place of residence, hypertension, diabetes, dyslipidemia, and chronic obstructive pulmonary disease.

vessels [34]. Additionally, cardiac-origin embolism could be the cause of stroke after thoracic radiation [31]. Furthermore, several studies show that chemotherapy with cisplatin may also cause acute and late arterial thrombosis [24,30,32]. It was found that chemotherapy led to vascular damages accompanying an increase in intima-media thickness and plasma von Willebrand factor levels [33]. In our study, patients receiving radiotherapy were at a higher CV risk than patients who received chemotherapy. However, it should be interpreted cautiously that radiotherapy may represent a higher risk than chemotherapy since radiotherapy was recommended for patients with multiple comorbidities who may already be more susceptible to CV risks. Those receiving both radiotherapy and chemotherapy were at the highest risk. It can be inferred that radiotherapy and chemotherapy may have a synergistic impact on developing an arterial thromboembolism. Our study implies that more attention should be paid towards CV risk in those who receive radiotherapy and/or chemotherapy.

Stratified analyses performed on the CV event-free survival period showed that the risk of CV events in lung cancer survivors were similar to those of the general population after a 5-year CV event-free period following treatment. With similar results to our study, nationwide follow-up studies from Sweden [9,10] reported that lung cancer was associated with the highest risk of CHD during the early survivorship period (standardized incidence ratio [SIR] = 2.56 at < 6 months and SIR = 1.38 at 6–12 months). After this period, the risk gradually decreased (SIR = 1.16 at 1–5 years, and SIR = 1.29 at 5–10 years), but was still higher than the general population for at least 10 years post-diagnosis [9]. In the case of IS, lung cancer patients showed a higher risk of stroke during the early survivorship period (SIR = 2.2 at < 6 months and SIR = 1.3 at 6–12 months), with no significant differences in stroke incidences during the 1–5 years and 5–10 years periods after diagnosis [10]. A nationwide study from Taiwan [15] also demonstrated that the risk of subsequent stroke increased within a 1–2 year period following diagnosis, and thereafter decreased to a similar level as seen in the general population, as was also the case in our study.

Thus, our findings and those from other national studies, suggest that a more meticulous management of CV risk should be given to lung cancer survivors during the early survivorship period, along with continued oncologic follow-ups.

Our study has several clinical implications; lung cancer survivors need to be given careful attention towards CV risk during the early survivorship period, and this attention should be continued long-term. To clarify, as cardiovascular-specific mortality becomes an increasingly important cause of mortality over the course of follow-up, especially in elderly patients [35,36], it is essential for lung cancer survivors to manage factors leading to CVD. However, thoracic surgeons and/or medical/radiological oncologists usually do not include cardiovascular management in their routine care. This is especially the case in Korea where the average oncology consultation time is 7–8 min on average [37], making it difficult for oncologic surgeons to manage all survivorship cases.

One solution for this is the shared care model suggested by Oeffinger et al. [38]. In this model, oncologists and primary care physicians (PCP) continue to communicate after cancer treatments, sharing the responsibility of care, as well as treatment summaries and care plans provided by oncologists to the PCP. In light of our study's findings, we suggest that patients should be referred to the PCP during the early survivorship period with treatment information and general recommendations; this will allow for the long-term management of cardiovascular risk by the PCP.

4.1. Limitations

There were several limitations to our study. First, this was a retrospective administrative data study. Second, as we used administrative data, we unfortunately did not have detailed clinical information on chemotherapy or radiotherapy regimens, cancer stage and recurrence. Cancer recurrence and subsequent mortality may compete with cardiovascular events. However, to minimize bias from this, we excluded all

subjects who were followed-up < 1-year post-lung cancer surgery and used competing risk models for sensitivity analyses. In addition, the results categorized by the CV event-free survival period showed that the risk of CV events last for a long time after surgery, regardless of cancer recurrence. Third, owing to the limitations of the administrative data of the KNHIS, the study population had a median follow-up period of approximately 4 years. A longer-term follow-up study is needed to confirm the long-term risk of CVD. Finally, our study is based on an Asian population in which prevalence of obesity and risk of CHD is much lower than that of Western populations. Therefore, our results need to be replicated in other ethnic groups.

4.2. Conclusions

In conclusion, our study showed an increased risk of CHD and stroke incidences among lung cancer patients who received curative surgery compared to the general non-cancer population; the level of risk was still similar when competing mortality from lung cancer was further considered. Chemotherapy and radiotherapy were associated with a higher risk, with a higher risk during the early survivorship period that persisted regardless of the survival period. Careful attention to CV risk for lung cancer survivors is therefore suggested, especially in those who receive chemotherapy and/or radiotherapy and should be considered during both the early survivorship and long-term survivorship periods.

Declaration of Competing Interest

None.

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None.

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