Current Problems in Cancer 45 (2021) 100615

Contents lists available at ScienceDirect

Current Problems in Cancer

journal homepage: www.elsevier.com/locate/cpcancer

Cardiovascular risk and undertreatment of dyslipidemia in lung cancer survivors: A nationwide population-based study

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ABSTRACT

Background: In lung cancer survivors, cardiovascular diseases (CVDs) are the leading cause of noncancer deaths. Nonetheless, there is lack of information on management of dyslipidemia, a major risk factor for future CVD events, in lung cancer survivors. This study aimed to assess dyslipidemia management and prevalence of statin eligibility in lung cancer survivors.
Methods: From the Korean National Health Insurance Service database, we selected 7349 lung cancer survivors who received surgery for lung cancer from 2007 to 2014. We used descriptive statistics for analy-

☆ Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors
☆☆ Declarations of interest: The authors declare that they have no competing interests to disclose.
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https://doi.org/10.1016/j.currproblcancer.2020.100615

ses of dyslipidemia management status on the basis of the National Cholesterol Education Program Adult Treatment Panel III guidelines. We also identified those who met the criteria for treatment on the basis of CVD risk according to the 2018 American College of Cardiology and American Heart Association (ACC/AHA) guidelines.

Results: The overall awareness and treatment rates for lung cancer survivors with dyslipidemia were 31.8% and 29.7%, respectively. The overall control rate for those receiving treatment was 88.7%, but was lowest in the highest risk group (78.1%). Furthermore, undertreatment of dyslipidemia was more prominent in young, male lung cancer survivors and those diagnosed with lung cancer within 3 years. Among those not receiving treatment for dyslipidemia, 61.7% were indicated for statin according to the ACC/AHA guidelines.

Conclusion: Over half of lung cancer survivors were not receiving treatment, although they were eligible for statin under current guidelines. To reduce noncancer mortality, statin use and adequate management of CVD risk factors should be encouraged in lung cancer survivors.

ARTICLE INFO

Keywords: Lung cancer; Cardiovascular disease; Dyslipidemia; Statin; Cancer survivor

Introduction

Lung cancer is currently the most commonly diagnosed type of cancer worldwide, according to 2018 global cancer statistics.[1] Furthermore, the 5-year survival rate for lung cancer is increasing,[2] and with increasing number of lung cancer survivors, management of other noncancer comorbidities is becoming important for this population. Studies on long-term lung cancer survivors have shown that the most common cause of noncancer death were cardiac diseases[3] and circulatory diseases (28.0% of noncancer deaths in >5-year survivors).[4] In addition, studies comparing shorter term lung cancer survivors to noncancer controls have also found that they have higher risk for cardiovascular diseases.[5,6] Therefore, the management of risk factors for cardiovascular diseases (CVDs) is essential for the care of lung cancer survivors.

The management of dyslipidemia in patients with high CVD risk is crucial for primary prevention of CVD.[7,8] Furthermore, statins, the mainstay of treatment for dyslipidemia, have been related with reduced cancer mortality[9] and suggested to have anticancer effects on cancer cells.[10] Statins have also been associated with improved survival in non–small-cell lung cancer (NSCLC) patients, further suggesting their potential anticancer effects.[11] Therefore, statin use in lung cancer survivors with dyslipidemia, especially those with high atherosclerotic cardiovascular disease (ASCVD) risks, may be important for the comprehensive care of these survivors.

Nonetheless, to the best of our knowledge, no studies have examined the treatment status of dyslipidemia in lung cancer survivors. Therefore, this study aimed to examine dyslipidemia management in lung cancer survivors using a nationwide population-based database, on the basis of the National Cholesterol Education Program Adult Treatment Panel (NCEP-ATP) III and the 2018 American College of Cardiology/American Heart Association (ACC/AHA) guidelines.[7,12]

Patients and methods

Data source

The Korean National Health Insurance Service (KNHIS) provides healthcare service coverage for all Koreans except Medical Aid beneficiaries (a total of 3% with the lowest income). Because physicians are reimbursed after the provision of medical services, the KNHIS contains data re-

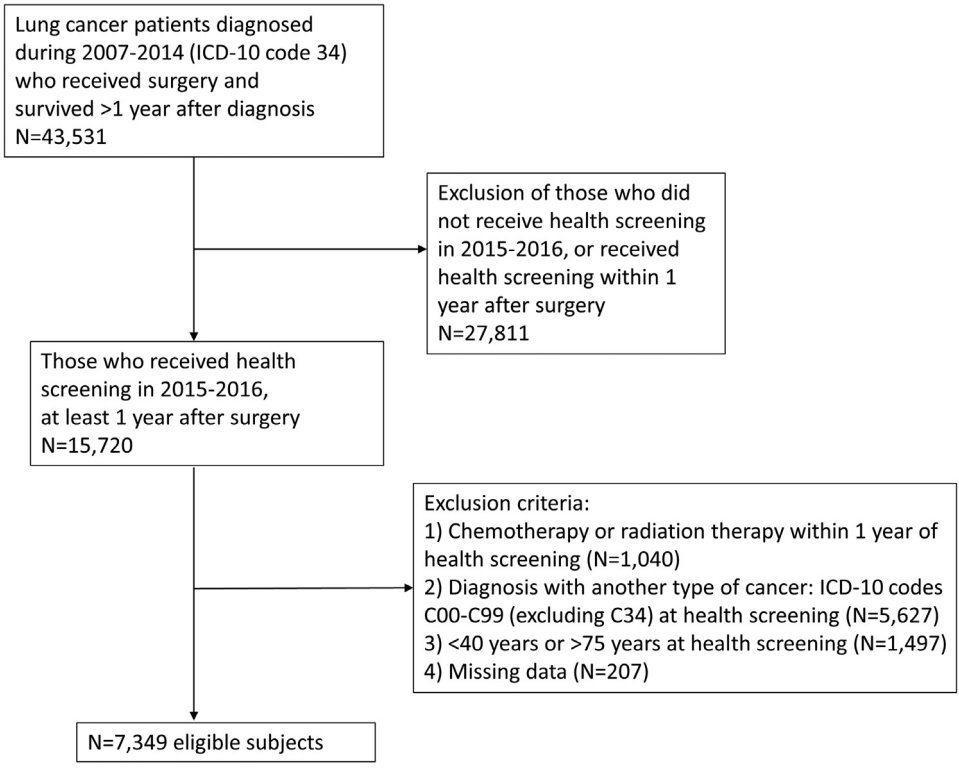

Figure 1. Study subjects' selection process.

quired for reimbursement, which include disease codes and medical services delivered. It also contains demographic data, as well as health-screening data. The KNHIS database has been used in many epidemiologic studies, and details can be found elsewhere.[13-15]

A total of 43,531 patients diagnosed with lung cancer between 2007 and 2014 (identified through the International Classification of Diseases (ICD)-10 code 34) received surgery and survived for over one year after diagnosis. After exclusion of patients according to criteria specified in Figure 1, 7349 lung cancer survivors were included in our analysis. We received approval for this study from the Institutional Review Board (IRB) at the Samsung Medical Center. Informed consent for the subjects was waived because this study was based on unidentifiable data (IRB No. SMC 2019-08-027).

Measurement and data collection

The KNHIS provides health screening for Koreans over 40 years old every 2 years, and employees of any age. The examinations include a self-reported questionnaire on past and current medical history, anthropometric measurements, and laboratory tests. Blood tests are performed after overnight fasting.

The prevalence of dyslipidemia was based on information regarding diagnosis and treatment for dyslipidemia and on lipid levels at the health examinations, on the basis of the NCEP-ATP III, which are also the treatment targets that physicians follow in Korea: (1) low-density lipoprotein cholesterol (LDL-C) $\geq$ 100 mg/dL in the presence of CVD or diabetes mellitus (DM); (2) LDL-C $\geq$ 130 if $>$ 2 risk factors; and (3) LDL-C $\geq$ 160 if 0-1 risk factor.[12]

Hypertension was assessed through blood pressure (BP) measurements at the health-screening examinations (systolic BP (SBP) ≥ 140 mm Hg or diastolic BP (DBP) ≥ 90 mm Hg) and information on past medical history. DM was determined through fasting blood glucose measurements at the health screening examinations (fasting blood sugar (FBS) ≥ 126 mg/dL) and information on past medical history.

Other cardiovascular risk factors were smoking, low high-density lipoprotein cholesterol (HDL-C), age, family history of CVD, and coronary heart disease (CHD). Smoking status was divided into current, past, or nonsmoker categories. CHD was defined through ICD-10 codes I20-25 recorded during hospitalization and past medical history. Low HDL-C, as a risk factor, was identified through blood levels of HDL-C < 40 mg/dL. HDL-C ≥ 60 mg/dL was considered as a protective factor for CVD.

Statistical analysis

We used descriptive statistics for characterization of the study subjects. All the analyses were performed using SAS statistical software (version 9.4; SAS Institute, Inc., Cary, NC).

Awareness, treatment, and control

Awareness was defined by subjects' report of diagnosis of dyslipidemia, among those with dyslipidemia. Treatment was defined by subjects' report of treatment for dyslipidemia, among those with dyslipidemia. Control was determined by blood cholesterol levels below the treatment criteria on the basis of the NCEP-ATP III for the risk groups. Awareness, treatment, and control of hypertension and DM were defined similarly as those of dyslipidemia (shown in Supplementary Table 1).

Determination of indication for dyslipidemia management among those currently not on treatment

We assessed whether a subject was indicated for statin therapy on the basis of the 2018 ACC/AHA cholesterol treatment guidelines among those not receiving treatment for dyslipidemia: (1) clinical ASCVD (ischemic heart disease or stroke); (2) LDL-C ≥ 190 mg/dL; (3) DM and LDL-C ≥ 70 mg/dL; (4) 10-year ASCVD risk score ≥7.5%.[16] Nonetheless, because the risk assessment tool in the ACC/AHA guideline was developed for Western populations, the risk may have been overestimated for East Asian populations. Therefore, we calculated the 10-year ASCVD risk scores with the use of the recalibrated Framingham risk equation developed for non-Chinese Asian populations[17] and the Korean Coronary Heart Disease risk score (KRS)[18] for sensitivity analyses.

Results

Characteristics of the study population

The study population comprised a total of 7349 subjects, with 4312 men and 3037 women, with the mean age at 59.4 ± 7.8 years. Those with longer interval since diagnosis of lung cancer were younger. Among the four surgery types, the majority received lobectomy (85.3%), 24.0% chemotherapy, and 6.6% radiation therapy (Table 1).

Table 1
Baseline characteristics of the study population.

	Total	By sex		By age at examination			By year since diagnosis of lung cancer		
	N (%) /mean ± SD	Male N (%) /mean ± SD	Female N (%) /mean ± SD	40-59 N (%) /mean ± SD	60-69 N (%) /mean ± SD	70- N (%) /mean ± SD	1-3 years N (%) /mean ± SD	3-5 years N (%) /mean ± SD	>5 years N (%) /mean ± SD
N	7349	4312	3037	2122	3323	1904	2463	2425	2461
Age at diagnosis, mean (SD)	59.4±7.8	59.9±7.7	58.6±7.8	49.9±4.9	60.5±3.5	68.1±2.6	60.6±8.0	59.7±7.7	57.8±7.4
40-59	3437 (46.8)	1881 (43.6)	1556 (51.2)	2122 (100.0)	1315 (39.6)	-	1014 (41.2)	1085 (44.7)	1338 (54.4)
60-69	3280 (44.6)	2030 (47.1)	1250 (41.2)	-	2008 (60.4)	1272 (66.8)	1055 (42.8)	1106 (45.6)	1119 (45.5)
70-	632 (8.6)	401 (9.3)	231 (7.6)	-	-	632 (33.2)	394 (16.0)	234 (9.7)	4 (0.2)
Comorbidity									
CHD	144 (2.0)	107 (2.5)	37 (1.2)	14 (0.7)	70 (2.1)	60 (3.2)	54 (2.2)	48 (2.0)	42 (1.7)
Stroke	33 (0.5)	24 (0.6)	9 (0.3)	2 (0.1)	13 (0.4)	18 (1.0)	6 (0.2)	9 (0.4)	18 (0.7)
COPD	1795 (24.4)	1195 (27.7)	600 (19.8)	341 (16.1)	819 (24.7)	635 (33.4)	668 (27.1)	585 (24.1)	542 (22.0)
Income									
Highest quartile	2673 (36.4)	1553 (36.0)	1120 (36.9)	781 (36.8)	1039 (31.3)	853 (44.8)	887 (36.0)	855 (35.3)	931 (37.8)
3nd quartile	1839 (25.0)	1088 (25.2)	751 (24.7)	502 (23.7)	916 (27.6)	421 (22.1)	613 (24.9)	603 (24.9)	623 (25.3)
2nd quartile	1350 (18.4)	833 (19.3)	517 (17.0)	423 (19.9)	646 (19.4)	281 (14.8)	472 (19.2)	451 (18.6)	427 (17.4)
Lowest quartile	1418 (19.3)	806 (18.7)	612 (20.2)	391 (18.4)	685 (20.6)	342 (18.0)	457 (18.6)	499 (20.6)	462 (18.8)
Medical aids	69 (0.9)	32 (0.7)	37 (1.2)	25 (1.2)	37 (1.1)	7 (0.4)	34 (1.4)	17 (0.7)	18 (0.7)
Place of residence									
Metropolitan	4435 (60.4)	2505 (58.1)	1930 (63.6)	1372 (64.7)	1992 (60.0)	1071 (56.3)	1520 (61.7)	1458 (60.1)	1457 (59.2)
City	2074 (28.2)	1247 (28.9)	827 (27.2)	588 (27.7)	936 (28.2)	550 (28.9)	662 (26.9)	695 (28.7)	717 (29.1)
Rural	840 (11.4)	560 (13.0)	280 (9.2)	162 (7.6)	395 (11.9)	283 (14.9)	281 (11.4)	272 (11.2)	287 (11.7)
Surgery									
Wedge	1202 (16.4)	656 (15.2)	546 (18.0)	393 (18.5)	523 (15.7)	286 (15.0)	450 (18.3)	415 (17.1)	337 (13.7)
Segmentectomy	301 (4.1)	165 (3.8)	136 (4.5)	100 (4.7)	121 (3.6)	80 (4.2)	154 (6.3)	94 (3.9)	53 (2.2)
Lobectomy	6272 (85.3)	3660 (84.9)	2612 (86.0)	1750 (82.5)	2865 (86.2)	1657 (87.0)	2030 (82.4)	2067 (85.2)	2175 (88.4)
Pneumonectomy	174 (2.4)	160 (3.7)	14 (0.5)	43 (2.0)	84 (2.5)	47 (2.5)	35 (1.4)	49 (2.0)	90 (3.7)
Chemotherapy	1760 (24.0)	1283 (29.8)	477 (15.7)	483 (22.8)	831 (25.0)	446 (23.4)	518 (21.0)	543 (22.4)	699 (28.4)
Radiation therapy	485 (6.6)	391 (9.1)	94 (3.1)	146 (6.9)	228 (6.9)	111 (5.8)	135 (5.5)	159 (6.7)	191 (7.8)
Treatment combination									
Surgery only	5486 (74.7)	2950 (68.4)	2536 (83.5)	1616 (76.2)	2442 (73.5)	1428 (75.0)	1921 (78.0)	1851 (76.3)	1714 (69.7)
Surgery + CTx	1378 (18.8)	971 (22.5)	407 (13.4)	360 (17.0)	653 (19.7)	365 (19.2)	407 (16.5)	415 (17.1)	556 (22.6)
Surgery + RT	103 (1.4)	79 (1.8)	24 (0.8)	23 (1.1)	50 (1.5)	30 (1.6)	24 (1.0)	31 (1.3)	48 (2.0)
Surgery + CTx + RT	382 (5.2)	312 (7.2)	70 (2.3)	123 (5.8)	178 (5.4)	81 (4.3)	111 (4.5)	128 (5.3)	143 (5.8)

CHD, coronary heart disease; COPD, chronic obstructive pulmonary disease; CTx, chemotherapy; N, number; RT, radiation therapy; SD, standard deviation.
Data are presented as number and percentages or mean and standard deviations.

Prevalence, awareness, and treatment status of dyslipidemia

The overall prevalence rate for dyslipidemia was 30.8%. The awareness and treatment rates were 31.8% and 29.7%, respectively, which were higher in women and those over 60 years old. Also, the control rate for those with dyslipidemia regardless of treatment was 27.7%, and among those who received treatment 88.7%.

On the basis of the different CVD risk groups, prevalence was highest among those with CHD or DM (53.3%). Nonetheless, awareness, treatment, and control rates were highest in the lowest risk group (Table 2).

Subjects indicated for statin and ASCVD risk scores among those not currently on treatment

Of the 7349 subjects, 9.2% were under dyslipidemia treatment and the remaining 90.8% were not receiving treatment. On the basis of the 2018 ACC/AHA treatment guidelines, over half (61.7%) of the remaining lung cancer survivors were indicated for treatment with statin because of the following: 2.3% had established CVD; 2.1% had LDL-C $\geq$ 190 mg/dL; 9.1% had DM and LDL-C between 70 and 189 mg/dL; and 59.7% had ASCVD risk scores $\geq$7.5%. More men than women were indicated for statin (76.7% vs 34.4%). Furthermore, the percentage of those who required statin rose with increasing age and with increase in the interval since lung cancer diagnosis. Similar results were obtained when we calculated the ASCVD risk scores using the recalibrated Framingham risk equation and the KRS criteria (Table 3).

Risk factors for cardiovascular disease in lung cancer survivors

The prevalence, awareness, and treatment rates for hypertension were 40.1%, 83.4%, and 80.1%, respectively. Among those with hypertension, the BP control rate regardless of treatment status was 59.9%, and among those receiving treatment 71.7%. The prevalence, awareness, and treatment rates for DM were 18.4%, 79.2%, and 75.1%, respectively. Among those with DM, the control rate regardless of treatment status was 38.0%, and among those receiving treatment 47.7%. A total of 33.7% were obese or severely obese, 4.3% current smokers, 24.9% current drinkers, and 29.2% performed regular physical activity (Supplementary Table 1).

Discussion

To the best of our knowledge, this is the first study to focus on the evaluation of dyslipidemia management in lung cancer survivors with the use of a nationwide population-based database. Our study shows that Korean lung cancer survivors receive suboptimal management for dyslipidemia. Those with overall prevalence of dyslipidemia who require treatment on the basis of the NCEP-ATP III risk groups was 30.8%, but only a quarter of them received treatment. Although the prevalence was higher in the high-risk group, it was less likely to be in adequate control. Among those who did not receive treatment for dyslipidemia, over half (around 60%) were indicated for statin on the basis of the 2018 ACC/AHA cholesterol treatment guidelines.

Management of dyslipidemia

The prevalence of dyslipidemia in our study of lung cancer survivors, 30.8%, was comparable to previous studies which used Korean National Health and Nutrition Survey (KNHANES) data and reported a prevalence of around 40% in Korean adults over 30 years old.[8-19] Regarding the three chronic diseases (hypertension, DM, and dyslipidemia) that need to be managed for

Table 2
Awareness and management of dyslipidemia by cardiovascular risk groups (according to National Cholesterol Education Treatment Program Adult Treatment Panel III criteria).

Total	Total	By sex		By age at examination			By year since diagnosis of lung cancer		
	N (%)	Male N (%)	Female N (%)	40-59 N (%)	60-69 N (%)	70- N (%)	1-3 years N (%)	3-5 years N (%)	>5 years N (%)
All patients	7349	4312	3037	2122	3323	1904	2463	2425	2461
Prevalence[a]	2262 (30.8)	1279 (29.7)	983 (32.4)	500 (23.6)	1120 (33.7)	642 (33.7)	771 (31.3)	722 (29.8)	769 (31.2)
Awareness	719 (31.8)	349 (27.3)	370 (37.6)	122 (24.4)	380 (33.9)	217 (33.8)	225 (29.2)	243 (33.7)	251 (32.6)
Treatment	672 (29.7)	323 (25.3)	349 (35.5)	111 (22.2)	354 (31.6)	207 (32.2)	206 (26.7)	229 (31.7)	237 (30.8)
Control[b]	626 (27.7)	306 (23.9)	320 (32.6)	110 (22.0)	330 (29.5)	186 (29.0)	188 (24.4)	219 (30.3)	219 (28.5)
Control among treated[c]	596 (88.7)	289 (89.5)	307 (88.0)	102 (91.9)	315 (89.0)	179 (86.5)	177 (85.9)	208 (90.8)	211 (89.0)
CHD or DM, LDL-C≥100	1447	1043	404	219	722	506	474	470	503
Prevalence[a]	771 (53.3)	522 (50.0)	249 (61.6)	128 (58.5)	382 (52.9)	261 (51.6)	256 (54.0)	245 (52.1)	270 (53.7)
Awareness	224 (29.1)	137 (26.3)	87 (34.9)	28 (21.9)	117 (30.6)	79 (30.4)	75 (29.3)	74 (30.2)	75 (27.8)
Treatment	215 (27.9)	131 (25.1)	84 (33.7)	27 (21.1)	113 (29.6)	75 (28.7)	71 (27.7)	72 (29.4)	72 (26.7)
Control (LDL<100)[b]	173 (22.4)	108 (20.7)	65 (26.1)	24 (18.8)	90 (23.6)	59 (22.6)	54 (21.1)	63 (25.7)	56 (20.7)
Control among treated[c]	168 (78.1)	106 (80.9)	62 (73.8)	24 (88.9)	87 (77.0)	57 (76.0)	52 (73.2)	61 (84.7)	55 (76.4)
≥2 Risk factors, LDL-C≥130	2010	1365	645	418	966	626	642	665	703
Prevalence[a]	777 (38.7)	459 (33.6)	318 (49.3)	152 (36.4)	379 (39.2)	246 (39.3)	252 (39.3)	256 (38.5)	269 (38.3)
Awareness	208 (26.8)	105 (22.9)	103 (32.4)	26 (17.1)	109 (28.8)	73 (29.7)	56 (22.2)	73 (28.5)	79 (29.4)
Treatment	199 (25.6)	100 (21.8)	99 (31.1)	24 (15.8)	104 (27.4)	71 (28.9)	53 (21.0)	70 (27.3)	76 (28.3)
Control (LDL<130)[b]	186 (23.9)	96 (20.9)	90 (28.3)	22 (14.5)	101 (26.7)	63 (25.6)	48 (19.1)	66 (25.8)	72 (26.8)
Control among treated[c]	180 (90.5)	93 (93.0)	87 (87.9)	21 (87.5)	97 (93.3)	62 (87.3)	46 (86.8)	63 (90.0)	71 (93.4)
≤1 Risk factors, LDL-C≥160	3892	1904	1988	1485	1635	772	1347	1290	1255
Prevalence[a]	714 (18.3)	298 (15.7)	416 (20.9)	220 (14.8)	359 (22.0)	135 (17.5)	263 (19.5)	221 (17.1)	230 (18.3)
Awareness	287 (40.2)	107 (35.9)	180 (43.3)	68 (30.9)	154 (42.9)	65 (48.2)	94 (35.7)	96 (43.4)	97 (42.2)
Treatment	258 (36.1)	92 (30.9)	166 (39.9)	60 (27.3)	137 (38.2)	61 (45.2)	82 (31.2)	87 (39.4)	89 (38.7)
Control (LDL<160)[b]	267 (37.4)	102 (34.2)	165 (39.7)	64 (29.1)	139 (38.7)	64 (47.4)	86 (32.7)	90 (40.7)	91 (39.6)
Control among treated[c]	248 (96.1)	90 (97.8)	158 (95.2)	57 (95.0)	131 (95.6)	60 (98.4)	79 (96.3)	84 (96.6)	85 (95.5)

CHD, coronary heart disease; DM, diabetes mellitus; LDL-C, low-density lipoprotein cholesterol; N, number; SD, standard deviation.
Risk factors were presence of hypertension, low high-density lipoprotein cholesterol (HDL-C, 40 mg/dL), current smoking, and family history of cardiovascular disease. Subtraction of 1 risk factor was done for high HDL-C (≥60 mg/dL).

[a] Prevalence: diagnosis of dyslipidemia, treatment for dyslipidemia or meeting the treatment criteria according to the National Cholesterol Education Treatment Program Adult Treatment Panel III risk categories.

[b] Control: among those with dyslipidemia, if previous CVD or DM then LDL <100 mg/dL, if >2 risk factors then LDL <130 mg/dL, if 0-1 risk factors then LDL <160 mg/dL.

[c] Control among treated: among those receiving treatment for dyslipidemia, if previous CVD or DM then LDL <100 mg/dL, if >2 risk factors then LDL <130 mg/dL, if 0-1 risk factors then LDL <160 mg/dL.

Table 3
Subjects indicated for statin and atherosclerotic cardiovascular disease (ASCVD) risk scores among lung cancer survivors currently not on treatment.

	Total	By sex		By age at examination			By year since diagnosis of lung cancer		
	N (%)	Male N (%)	Female N (%)	40-59 N (%)	60-69 N (%)	70- N (%)	1-3 years N (%)	3-5 years N (%)	>5 years N (%)
Total N, not on treatment (A)	6670	3989	2681	2004	2969	1697	2255	2194	2221
Treatment indicated									
established ASCVD (B)	151 (2.3)	110 (2.8)	41 (1.5)	14 (0.7)	68 (2.3)	69 (4.1)	52 (2.3)	51 (2.3)	48 (2.2)
LDL≥190 (C)	140 (2.1)	60 (1.5)	80 (3.0)	42 (2.1)	72 (2.4)	26 (1.5)	57 (2.5)	42 (1.9)	41 (1.9)
DM+LDL 70-189 (D)	606 (9.1)	428 (10.7)	178 (6.6)	81 (4.0)	304 (10.2)	221 (13.0)	201 (8.9)	185 (8.4)	220 (9.9)
ASCVD risk score ≥7.5% (E)[a]	3981 (59.7)	3061 (76.7)	920 (34.4)	307 (15.3)	1999 (67.3)	1675 (98.7)	1258 (55.8)	1295 (59.0)	1428 (64.3)
7.5%-10%	697 (17.5)	444 (14.5)	253 (27.5)	160 (52.1)	471 (23.6)	66 (3.9)	239 (19.0)	227 (17.5)	231 (16.2)
10%-20%	1951 (49.0)	1456 (47.6)	495 (53.8)	130 (42.4)	1140 (57.0)	681 (40.7)	631 (50.2)	657 (50.7)	663 (46.4)
20%-30%	858 (21.6)	724 (23.7)	134 (14.6)	14 (4.6)	281 (14.1)	563 (33.6)	254 (20.2)	271 (20.9)	333 (23.3)
30%-50%	438 (11.0)	401 (13.1)	37 (4.0)	2 (0.7)	100 (5.0)	336 (20.1)	126 (10.0)	126 (9.7)	186 (13.0)
≥50%	37 (0.9)	36 (1.2)	1 (0.1)	1 (0.3)	7 (0.4)	29 (1.7)	8 (0.6)	14 (1.1)	15 (1.1)
Sum of above indications[a] (B+C+D+E/A)	4112 (61.7)	3092 (77.5)	1020 (38.1)	385 (19.2)	2052 (69.1)	1675 (98.7)	1313 (58.2)	1330 (60.6)	1469 (66.1)
ASCVD risk score ≥7.5% (F)[b]	4120 (61.8)	2899 (72.7)	1221 (45.5)	244 (12.2)	2188 (73.7)	1688 (99.5)	1299 (57.6)	1350 (61.5)	1471 (66.2)
7.5%-10%	929 (22.6)	559 (19.3)	370 (30.3)	156 (63.9)	705 (32.2)	68 (4.0)	310 (23.9)	324 (24.0)	295 (20.1)
10%-20%	2361 (57.3)	1668 (57.5)	693 (56.8)	85 (34.8)	1307 (59.7)	969 (57.4)	749 (57.7)	777 (57.6)	835 (56.8)
20%-30%	683 (16.6)	547 (18.9)	136 (11.1)	2 (0.8)	157 (7.2)	524 (31.0)	198 (15.2)	201 (15.0)	284 (19.3)
30%-50%	146 (3.5)	125 (4.3)	21 (1.7)	1 (0.4)	19 (0.9)	126 (7.5)	42 (3.2)	47 (3.5)	57 (3.9)
≥50%	1 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.1)	0 (0.0)
Sum of above indications[b] (B+C+D+F)/A	4235 (63.5)	2940 (73.7)	1295 (48.3)	324 (16.2)	2223 (74.9)	1688 (99.5)	1350 (59.9)	1381 (62.9)	1504 (67.7)
ASCVD risk score ≥7.5% (G)[c]	3843 (57.6)	2584 (64.8)	1259 (47.0)	123 (6.1)	2023 (68.1)	1697 (100.0)	1203 (53.4)	1255 (57.2)	1385 (62.4)
7.5%-10%	932 (24.3)	563 (21.8)	369 (29.3)	85 (69.1)	814 (40.2)	33 (1.9)	286 (23.8)	322 (25.7)	324 (23.4)
10%-20%	2271 (59.4)	1536 (59.4)	735 (58.4)	37 (30.1)	1129 (55.8)	1105 (65.1)	734 (61.0)	736 (58.7)	801 (57.8)
20%-30%	564 (14.7)	427 (16.5)	137 (10.9)	0 (0.0)	74 (3.7)	490 (28.9)	160 (13.3)	167 (13.3)	237 (17.1)
30%-50%	75 (2.0)	58 (2.2)	17 (1.4)	1 (0.8)	6 (0.3)	68 (4.0)	23 (1.9)	29 (2.3)	23 (1.7)
≥50%	1 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.1)	0 (0.0)
Sum of above indications[c] (B+C+D+G)/A	3980 (59.7)	2652 (66.5)	1328 (49.5)	220 (11.0)	2063 (69.5)	1697 (100.0)	1263 (56.0)	1291 (58.8)	1426 (64.2)

ASCVD, atherosclerotic cardiovascular disease; DM, diabetes mellitus; KRS, Korean coronary heart disease risk score; LDL, low-density lipoprotein; N, number; SD, standard deviation.

[a] ASCVD risk score calculated by the 2018 American College of Cardiology/American Heart Association guidelines.

[b] ASCVD risk score calculated by recalibrated Framingham risk equation developed from results on non-Chinese Asian populations.

[c] ASCVD risk score calculated by the Korean coronary heart disease risk score.

prevention of CVD, lung cancer survivors had the lowest awareness and treatment rates for dyslipidemia. This finding is in agreement with an analysis of the general population that used the KNHANES data, where awareness and treatment rates were lower for dyslipidemia than for hypertension and diabetes.[19] The lack of awareness and consequent treatment may be due to the absence of symptoms, lack of awareness, and diagnosis requirement of overnight fasting blood examinations.[20]

Younger survivors who are less than 60 years old were less likely to be aware and receive treatment for dyslipidemia than those over 60. This indicates that younger patients are more prone to undertreatment for dyslipidemia, possibly because they are less aware and more likely to underestimate the importance of prevention of future CVD events and thus more reluctant to receive medication for dyslipidemia. Our results are in agreement with previous studies, which have revealed that younger patients have lower adherence to statin treatment.[21] This difference in age may also be due to higher frequency of medical contacts in the older age groups.[22]

Although the prevalence did not differ by sex, awareness and treatment rates of dyslipidemia were higher in women than men. These differences in sex have been observed in other population-based studies, where women show higher rates for awareness and treatment of dyslipidemia than men,[23] possibly because they may be more inclined to health-seeking behaviors.[24,25]

Although the prevalence did not differ regarding interval since diagnosis, the awareness, treatment, and control rates were lower in those diagnosed 1-3 years ago than those diagnosed over 3 years ago. Several studies have shown that lung cancer survivors have the highest CVD risk during the early survivorship period, which decreases or becomes similar to the general population during the later periods.[26,27] A recent Korean study also found that lung cancer survivors had increased CVD risk compared with the general population in the earliest 3 years and was especially highest in those who received both chemotherapy and radiotherapy.[5] Increased CVD risk in lung cancer survivors may be due to treatment, and previous studies have suggested that chemotherapy and radiotherapy can increase CVD risk through damage to the vessels, cardiotoxicity, and thrombosis.[28-30] Our results imply that lung cancer survivors who have received radiotherapy and chemotherapy and those in the early survivorship period may require more attention for dyslipidemia management.

On the basis of the NCEP-ATP III risk group categories for treatment of dyslipidemia, those with CHD or DM, who are at higher risk for CVD, had the highest prevalence rates but the lowest control rates for dyslipidemia. This indicates that even with treatment, the dosage of statin may have been inadequate for high-risk groups. This finding is in agreement with that of a study based on the Korean general population, where higher CVD risk levels were associated with higher prevalence and lower control rates for dyslipidemia.[19]

Undertreatment of dyslipidemia on the basis of ASCVD risk scores

Among those who did not receive treatment for dyslipidemia, around 60% had elevated CVD risk on the basis of the 2018 ACC/AHA cholesterol management guidelines and were indicated for statin therapy.[7,8] The total percentage of the risk groups who require treatment did not differ substantially regarding the method used for ASCVD risk score calculation. Besides the absolute LDL-C levels, the 10-year ASCVD risk score of over 7.5% (intermediate or high risk) is another important criteria for statin. Nonetheless, physicians often make treatment decisions based solely on the absolute LDL-C levels instead of considering other risk factors, such as age and ASCVD risk scores, which is probably owed to lack of time or awareness during clinical practice, as shown by an outpatient-based study, which found that treatment for dyslipidemia appeared to depend on LDL-C levels rather than calculated CV risk scores.[31] As a result, the need for dyslipidemia treatment may go unnoticed in the intermediate or high-risk groups with moderate or low LDL-C levels.

Other risk factors

Many lung cancer survivors had several risk factors for CVD, as over half (61.6%) were either overweight or obese, and only 29.2% of the total study population performed regular physical activity. Although smoking is a major known risk factor for both lung cancer and CVD, 4.3% were current smokers. Furthermore, among those receiving treatment for their specified condition, the control rates for hypertension (71.7%) and DM (47.7%), the other major risk factors for CVD, were lower than those for dyslipidemia (88.7%). These results suggest that the lung cancer survivors may have not been receiving appropriate management and prevention for CVD, although they usually maintain regular follow-ups with a lung cancer specialist after their diagnosis.

Clinical implications

Previous studies on long-term lung cancer survivors have shown that the most common cause of noncancer death were cardiovascular diseases. A US study using Surveillance, Epidemiology and End Results (SEER) data reported that the most common cause of noncancer death in >10-year lung cancer survivors was cardiac disease (6.9% of study participants), and a Korean study of >5-year lung cancer survivors also reported that the most common cause of noncancer death were circulatory diseases (28.0% of all noncancer deaths).[3,4] In addition, studies comparing shorter term lung cancer survivors to noncancer controls also showed that they have higher risk for cardiovascular diseases: a Swedish study found that CHD risk was increased for lung cancer patients within the first 6 months after diagnosis with a standardized incidence ratio of 2.56[27]; a US study using SEER data found that lung/bronchus cancer survivors with a median follow-up of 4.4 years had an incidence rate ratio of 1.58 for CVD events[6]; and a Korean study on lung cancer survivors with a median follow-up of 3.9 years reported an adjusted hazard ratio of 1.27 for CV events.[5] However, despite the increased CVD risk shown in previous studies, our study's results on the undertreatment of dyslipidemia show that management of CVD risk factors may be inadequate in lung cancer survivors.

Given that lung cancer survivors receive regular follow-ups after their diagnosis of lung cancer, especially for up to 5 years, our study results suggest that comprehensive management for prevention of CVD may have been overlooked in routine survivorship care. Lung cancer survivors, and perhaps also their physicians, may have lack of interest or motivation to treat dyslipidemia and may have focused only on lung cancer treatment. Nonetheless, comorbidity has been reported to affect the cancer survival, especially through independent effect on non-cancer mortality, and cancer therapies have been reported to increase CVD risk and worsen comorbidities.[32] Lung cancer and CVDs share common risk factors, such as smoking and aging, and lung cancer survival can also be affected by presence of CVDs.[33] Therefore, management and prevention of CVDs and its risk factors are important in lung cancer survivorship.[34]

Although some studies have found that cancer survivors have more chronic conditions and increased visits to primary care than those without cancer,[35] they may be negligent in the management of noncancerous diseases and shift their attention away from chronic medical conditions.[36,37] This may be due in part to high prioritization of treatment for the primary cancer and decreased interest by oncologists in the management of other noncancer diseases during the routine hospital visits.[38,39] The patients with cancer might also lose contact with other noncancer physicians, and previous studies have shown that decreased primary care physician (PCP) involvement leads to decreased appropriate health management.[40] The Current National Comprehensive Cancer Network (NCCN) guidelines state that the care of cancer survivors should include coordination between PCPs and specialists to ensure that all of the patient's health needs are met.[41] Although oncologists manage and follow-up the primary cancer, PCPs can assume responsibility for the other physical and emotional needs of the survivors.[42,43] The complexity of survivorship care and multiple challenges owing to coexistence of cancer and chronic conditions may require a multilevel approach.[32]

Limitations

This study has several limitations. First, because of administrative data utilization, we did not have access to detailed clinical information regarding cancer staging, type, and histologic diagnosis. Second, the diagnosis and treatment of dyslipidemia, hypertension, and DM used information from self-reported questionnaires, which may have been affected by recall bias. Finally, this study was based on the Korean population, and the results may not be generalizable to other ethnic populations or nations with different health systems.

Conclusion

This study shows that only 31.8% of Korean lung cancer survivors were aware of having dyslipidemia and only 29.7% of them received treatment. In addition, over half of the lung cancer survivors who were not receiving treatment were actually indicated for statin therapy. These results suggest that the lung cancer survivors may have not received adequate care for prevention of CVD and undertreatment is common. More attention by the physicians and the survivors themselves is necessary for optimal management of dyslipidemia.

Author contributions

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.currproblcancer.2020.100615.

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