김향경 석사 학위논문

National health insurance data analysis on association between abdominal aortic aneurysm and cancer

복부대동맥류와 암의 연관성에 대한 국민건강보험공단자료 분석

2021 년 2 월

서울대학교 대학원

보건학과 보건통계학전공

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지도교수 김 호

이 논문을 김향경 석사 학위논문으로 제출함

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서울대학교 대학원

보건학과 보건통계학전공

김 향 경

김향경의 석사 학위논문을 인준함

2021 년 1 월

위 원 장 조 성 일 (인)

부 위 원 장 원 성 호 (인)

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Abstract

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Background: Cancer and abdominal aortic aneurysm (AAA) each carry substantial morbidity and mortality and commonly develop in old age. In case of coexistence of both diseases, difficulty may be encountered to set up a treatment plan and long-term survival of patients with both disease tends to be lower compared to the patients with AAA alone. Clinical trials or observational studies with sufficient power to prove the association between them were limited because of relatively low frequency as well as slow disease process of both diseases. Therefore, we purposed to determine whether there is a significant association between abdominal aortic aneurysm and cancer with using nationwide data.

Material and methods: With using the national health insurance service-national sample cohort of South Korea, patients over 50 years who were diagnosed with AAA between 2002 and 2015, patients with heart failure (HF) and controls without AAA or HF matched by age, sex and cardiovascular risk factors were enrolled. Primary outcome was the incidence rates of cancer were assessed in participants with and without AAA. Secondary outcome was cancer related survival and cancer risk.

Results: A total of 823 patients with AAA, from 50 years (mean [SD] age, 71.8 [9.4] years; 552 [67.1%] men) and each matched 823 heart failure patients without AAA and controls without AAA were identified. The prevalence of cancer was 45.2% (372/823) in AAA group, 41.7% (343/823) in HF group, and 35.7% (294/823) in controls and it was significantly higher in AAA group than controls (*P* <.001). The risk of developing cancer was higher in patients with AAA than in control group (adjusted odds ratio 1.52 [95% CI, 1.24 - 1.86], *P* <.001), as in HF group (adjusted odds ratio 1.37 [1.24-1.86], *P* =.006). Cancer related -death rate per 100 person-years was 4.36 in AAA group, 4.16 in HF group and 3.43 in control and the mortality was 2.64 times higher ([95% CI, 2.22-3.13], *P* <001) for AAA group and 1.63 ([95% CI, 1.37-1.92], *P* <.001) for HF group than controls. Most common cause of death in AAA patients were cancer and cardiovascular disease. Conclusion: There was significantly increased risk of cancer in AAA patients than HF patients and controls during the 13 years of follow-up. Most common cause of death in AAA patients were cardiovascular disease and cancer. Therefore appropriate screening algorithm might be necessary for earlier detection of both diseases to improve long-term survival.

Key words: abdominal aortic aneurysm; cancer; mortality; cause of death; heart failure

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Introduction

An abdominal aortic aneurysm (AAA) is localized dilatation of the infrarenal aorta.[1] There is no definite consensus regarding the definition of AAA to date. The most widespread definition of an AAA is an abdominal aortic diameter of 3.0 cm or more or the maximum diameter of 50% greater than the suprarenal diameter.[2] AAAs cause 1·3% of all deaths among men aged 65–85 years in developed countries.[1] AAA is multifactorial disease with relation to both genetic and environmental risk factors.[3] Smoking is considered one of the most important risk factors for AAA.[4] Other risk factors include male sex, age, hypertension, chronic obstructive pulmonary disease, dyslipidemia and family history.[1] Prevalence is negligible before the age of 55-60 years and thereafter prevalence increases steadily with age.[5] Therefore most surveillance programs are targeting men aged 65 to 75 years.[6,7]

In an ageing population multimorbidity is frequent. Various diseases show an age-related prevalence and due to shared risk factors, some morbidities often coincide.[8] Concomitant cancer and AAA is a long-standing subject of study in deciding treatment priority and method.[9,10] The true incidence is difficult to determine accurately, but it has been reported between 0.49% and 38.1%.[10-14] Commonly reported types of associated cancer are including lung, colorectal, and prostate.[11,15-18] It was reported that the incidence of AAA was 100 times higher in comparison with the similar age group of men in the general population.[17] Similar phenomenon was observed in lung cancer patients.[16] Long-term survival rates have been reported to be lower when both diseases coexisted compared to the case with only AAA.[19] Traditionally, AAA is regarded as a consequence of atherosclerosis owing to its association with atherosclerotic change of the aortic wall.[20] However, recent studies have demonstrated medial and adventitial injury from proteolysis, oxidative stress and adaptive immune responses than atherosclerotic change.[21-23] Accumulating evidence suggests that oxidative stress and its direct consequences, including lipid peroxidation, are involved in numerous pathological states including atherosclerosis, cancer, and inflammation.[24] Concurrence may be attributable to similar patient demographics such as increasing age and male sex and common risk factors such as smoking,[25] or there may be a common pathway as suggested in other diseases.[26-28] High rate of coexistence should be elucidated to suggest simultaneous surveillance for improvement of long-term survival or to elucidate possible common pathogenesis or risk factors.

In this study, we purposed to investigate the prevalence of concomitant AAA and cancer in a national sample cohort from Korean population. In addition, the mortality rate related to AAA and the cause of death were analyzed.

Materials and Methods

Data sources

This study was undertaken using a national sample cohort (NSC) database that were acquired from the National Health Insurance Service (NHIS), from January 2002 to December 2017. The NHIS-NSC database is a population-based cohort established by the NHIS. This cohort includes approximately 2.2% of the eligible entire population, randomly sampled from 2002 National Health Insurance Recipient Qualifications Database and followed up to 2015. Each patient's demographic information, International Classification of Disease, Tenth Revision (ICD-10) diagnosis codes, procedure codes, and survival in inpatient and outpatient services were collected and analyzed. This study was exempted from review by the Seoul National University Hospital Institutional Review Board (SNU 20-07-074).

Study design and cohort definition

Study design is depicted in Figure 1. Patients with a first-time diagnosis of AAA (ICD-10 codes I713-714, 718) between January 2002 and December 2015 were identified. Patients with the following conditions were excluded: (1) abdominal aortic aneurysm related to Behcet's disease (ICD-10 code M352) or syphilis (ICD-10 code A539); (2) previous history of typhoid fever (ICD-10 code A01); (3) age younger than 50. The two control groups without AAA was randomly sampled from individuals who had not been diagnosed with AAA during the same period; one with heart failure (HF, [ICD-10 codes I500-509]) and the other without HF after matching for age, sex, and other cardiovascular risk factors such as hypertension, diabetes, and dyslipidemia (1:1:1 matching). The sex was matched completely, the age difference was less than 6 years old, and HTN, DM, and dyslipidemia were matched as possible.

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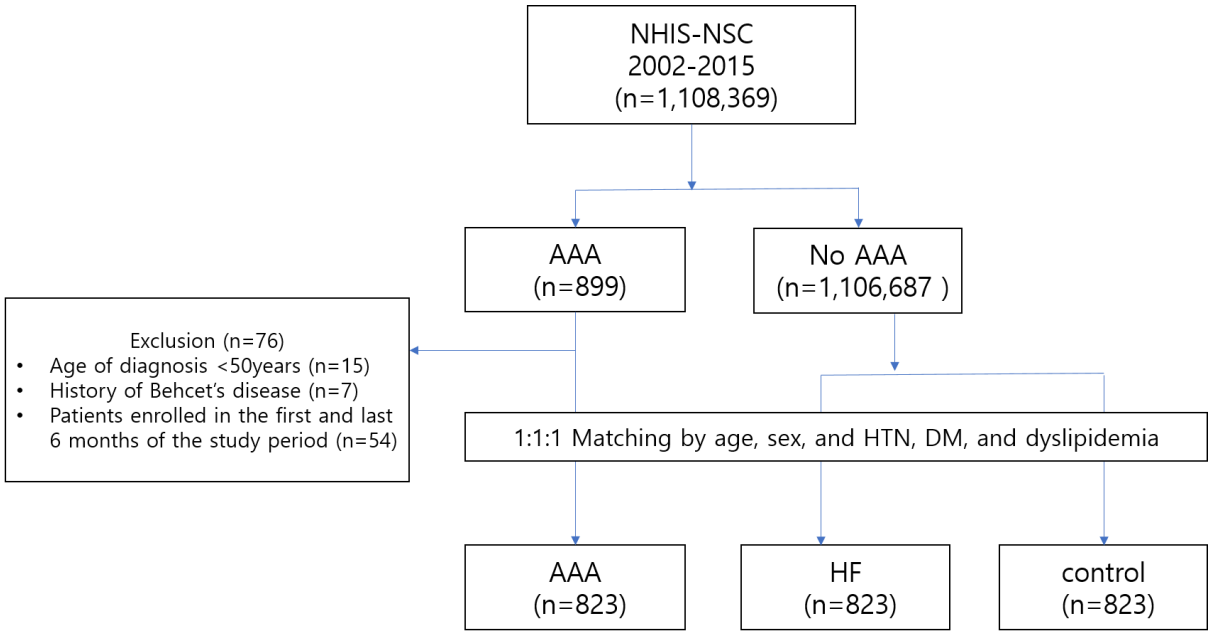
Figure 1 Flow diagram



NHIS-NSC, National Health Insurance Service-national sample cohort; AAA, abdominal aortic aneurysm; HTN, hypertension; DM, diabetes mellitus; HF, heart failure

To assess the diagnostic accuracy of the AAA cases registered in the database, we reviewed the image sets and medical records of randomly sampled patients at a single university hospital with using similar codes of AAA as well as AAA codes. For similar codes of AAA, we reviewed patients diagnosed with thoracoabdominal aortic aneurysm (I716), dissection of aorta (I710), thoracoabdominal aortic aneurysm, ruptured (I715), aortic aneurysm of unspecified site, without rupture (I719), aneurysm and dissection of iliac artery (I723), aneurysm and dissection of artery of lower extremity (I724), and aneurysm of aorta in diseases classified elsewhere (I790). One vascular surgeon reviewed the CT images and medical records for all registered and suspected cases in the hospital from January 1, 2018, to December 31, 2019. The vascular surgeon independently investigated whether registered and similar codes was matched the diagnosis for AAA and calculated the specificity and sensitivity.

The index date of each group was defined as the first diagnosis date of AAA or HF in the AAA and HF group respectively, and June 1 of the diagnosis year of the matched AAA patients in the control group.

Study outcome

The primary outcome was development of any cancer. Patients with cancer were defined as those who had 1 or more hospitalization, visited outpatient clinic at least twice or have the Special Support for Serious Illness act code with a principal or sub- diagnosis code of cancer (ICD-10 codes C00-97). The secondary outcome was the cause of death and the mortality rate per 100 person-years. Cancer diagnosis period was classified as follows based on index date; at least 6 months before the index date, within 6 months before and after the index date and 6 months after the index date (Figure 2). Cancer that occurred at least 6 months after the index date was defined as a newly developed cancer.

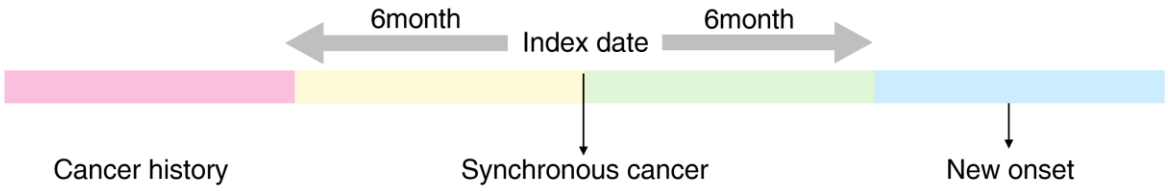


Figure 2. Diagnosis period of cancer based on the index date.

First, cancer risk was analyzed by including all cancer regardless of the period of occurrence. Then, the hazard ratio was calculated by analyzing patients with newly developed cancer among those who did not develop cancer until 6 months from the index date.

Statistics

Demographic data was compared by generalized estimating equation method with appropriate distributions for paired data. The association with cancer was analyzed by conditional logistic regression and the results were represented as odds ratios (OR) and 95% confidence intervals (CI). The incidence of cancer or death after enrollment were evaluated by incidence rate per 100 person-years and Kaplan-Meier curve analysis. Cox proportional hazard regression model with robust variance estimate considering paired data was used to determine the adjusted hazard ratio (HR) and corresponding 95% confidence intervals for the association between AAA and cancer. The cumulative survival probability was presented graphically by Kaplan–Meier curve. All p-values < .05 were considered significant. The statistical analysis was performed using SAS Enterprise guide version 7.1

(SAS Institute Inc., Cary, NC, USA) and R software version 3.0.3 (R Development Core Team, 2006).

Results

1. Baseline demographics

Characteristics of study population

When reviewed 2 352 patients' hospital data to verify the diagnostic accuracy of the ICD-10 codes containing I713-714 and I 718 detecting AAA patients, the sensitivity and specificity was 99.7% (642/644) and 99.6% (1650/1656). I719 codes were not utilized in this study since the misclassification rate was high: 35 patients out of 52 patients (67.3%) were not AAA patients. Among 1,108,369 subjects from the NHIS-NSC database, we identified 899 AAA patients and 61≥ of them were excluded from the analysis by the aforementioned criteria. Mean age of the AAA group was 71.8 years (standard deviation 9.4 years: range - years) and was composed of 32.9% (271) women and 62.2% (512) men. Among remaining 1,106,687 participants without AAA, through 1:1:1 matching, we included 823 patients of HF cohort and 823 of control cohort. Baseline characteristics of the three groups are summarized in Table 1.

Table 1. Baseline demographic data

	AAA (N=823)	Matched HF (N=823)	Matched Control (N=823)	***P***
Age (years), mean(SD)	71.8 (9.4)	71.6 (9.2)	71.8 (9.4)	0.903
Male, n(%)	552 (67.1)	552 (67.1)	552 (67.1)	>.999
Comorbidities				
Diabetes mellitus	512 (62.2)	487 (59.2)	512 (62.2)	<.001
Hypertension	716 (87.0)	717 (87.1)	716 (87.0)	0.607
Dyslipidemia	619 (75.2)	413 (50.2)	716 (87.0)	<.001
Alcohol*				0.087
None	372 (45.2)	256 (31.1)	362 (44.0)	
<3 days /week	111 (13.5)	79 (9.6)	148 (18.0)	
≥3 days /week	71 (8.6)	51 (6.2)	82 (10.0)	
Missing	269 (32.7)	437 (53.1)	231 (28.1)	
Smoking*				<.001
Non-smoker	286 (34.8)	261 (31.7)	390 (47.4)	
Ex-smoker	64 (7.8)	47 (5.7)	90 (10.9)	
Current smoker	204 (24.8)	79 (9.6)	112 (13.6)	
Missing	269 (32.7)	436 (53.0)	231 (28.1)	

*Smoking and alcohol history was obtained from the general health check-up data from the index year to the following year.

Abdominal aortic aneurysm

Total 211 patients (25.6%) underwent procedures: endovascular aneurysm repair (EVAR) in 134 (60.4%) and open surgical repair in 77 (34.7%). Procedure related outcome is described in Table 2.

Table 2. Postoperative outcome in AAA group

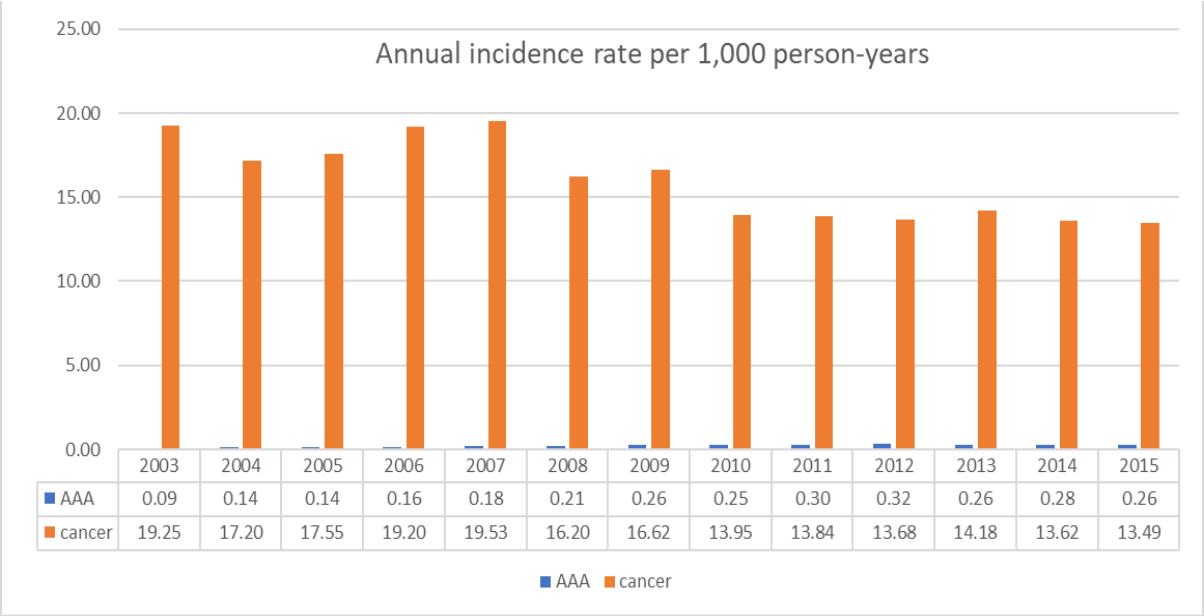
	Total	**OSR**	**EVAR**	p
Total	211	77	134	
No. of death	64	24	40	
Mortality (%) (95% CI)	57.7 (43.0 - 72.5)	53.6 (36.1 - 71.1)	44.3 (29.9 - 58.7)	
Death rate per 100 person-years	8.39	5.93	11.17	
Unadjusted HR (95% CI)		1 (Reference)	1.76 (1.02 - 3.03)	0.044
Adjusted[a] HR (95% CI)		1 (Reference)	1.22 (0.69 - 2.17)	0.498
Ruptured	23	11	12	
No. of death	13	6	7	
Mortality (%) (95% CI)	85.3 (61.3 - 100)	79.6 (46.4 - 100)	58.3 (30.4 - 86.2)	
Death rate per 100 person-years	17.88	10.25	49.44	
Unadjusted HR (95% CI)		1 (Reference)	7.91 (0.97 - 64.64)	0.054
Adjusted[a] HR (95% CI)		1 (Reference)	14.58 (0.99 - 215.69)	0.051
Unruptured	188	66	122	
No. of death	51	18	33	
Mortality (%) (95% CI)	53.9 (37.2 - 70.6)	48.7 (29.1 - 68.3)	42.0 (27.0 - 57.0)	
Death rate per 100 person-years	7.39	5.20	9.59	
Unadjusted HR (95% CI)		1 (Reference)	1.75 (0.94 - 3.28)	0.080
Adjusted[a] HR (95% CI)		1 (Reference)	1.07 (0.55 - 2.08)	0.833

[a] adjusted by hypertension, diabetes, dyslipidemia

2. Association between AAA and cancer

Annual incidence of AAA and cancer

The annual incidence of AAA was 0.09-0.26 per 1,000 person-years (Figure 3). From 2003 to 2012, it increased steadily, but reached a plateau from 2013 to 2015.



	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
AAA	0.09	0.14	0.14	0.16	0.18	0.21	0.26	0.25	0.30	0.32	0.26	0.28	0.26
cancer	19.25	17.20	17.55	19.20	19.53	16.20	16.62	13.95	13.84	13.68	14.18	13.62	13.49

Figure 3. Annual incidence of AAA and cancer

Incidence of cancer

A total of 372 (45.2%) AAA, 343 (41.37%) HF, and 294 (35.7%) controls were diagnosed with malignant cancer ($p < .001$). The type of cancer and the period when the patient was diagnosed with cancer in relation to the index date is described in Table 3.

Table 3. Cancer diagnosis period based on index date in each group.

	AAA (N=823)		Matched HF (N=823)		Matched Control (N=823)		*p*
Cancer							<.001
No	451	(54.8)	480	(58.3)	529	(64.3)	
Yes	372	(45.2)	343	(41.7)	294	(35.7)	
Cancer diagnosis period based on index date							<.001
Before 6 months	177	(21.5)	97	(11.8)	166	(20.2)	
Within 6 months to index date	56	(6.8)	18	(2.2)	27	(1.8)	
From the index date up to 6 months	47	(5.7)	29	(3.5)	12	(1.5)	
After 6 months	92	(11.2)	199	(24.2)	101	(12.3)	
Types of cancer							
Lung	57	(15.3)	67	(19.5)	34	(11.6)	
Colorectal	116	(31.2)	38	(11.1)	37	(12.6)	
Hematologic	12	(3.2)	7	(2.0)	2	(0.7)	
Other solid tumor*	187	(50.3)	231	(67.3)	221	(75.2)	

Each cell is presented by n (%).

AAA, abdominal aortic aneurysm; HF, heart failure

*Breast and genitourinary cancers are included

177 (21.5%) of the patients with AAA had malignancies before the diagnosis of AAA (Table 3). Malignancies were found in 103 (12.5%) patients within 6 months from the diagnosis of AAA and in 92 (11.2%) patients 6 months after diagnosis of AAA. In HF group, 97 patients (11.8%) of patients had cancer history before the diagnosis of HF and 47 (5.7%) patients was diagnosed with cancer within 6 months from the diagnosis of the HF. Newly diagnosed cancer was found in 199 (24.2%) patients in HF group 6 months after the diagnosis of the HF. In control group, 166 patients (20.2%) of patients had cancer history before the index date and 27 (3.3%) patients was diagnosed with cancer

within 6 months from the diagnosis of the index date. Newly diagnosed cancer was found in 101 (12.3%) patients in controls 6 months after the index date.

In the main diagnostic codes of NHIS-NSC database, breast and genitourinary cancer clustered with other cancers indistinguishable because of the privacy issue. Among identifiable types of cancer, most common type of cancer in AAA group was colorectal cancer (31.2%, 116/372), followed by lung cancer (15.3%, 57/372). The most common cancer in the HF and the control group was lung cancer, accounting for 19.5% (67/343) and 11.6% (34/294), respectively.

Comparison of the risk of cancer between the groups

Cancer risk was analyzed by cancer prevalence rate in each group. The risk of cancer was 1.50 times (95% CI, 1.23 - 1.83) in the AAA group and 1.29 times (95% CI, 1.06 - 1.58) in the HF group compared to the control group (*P*<.001) (Table 4). The risk of cancer was significantly higher in AAA group regardless of adjustment. When adjusted by hypertension, diabetes, dyslipidemia and smoking, the risk of cancer was 1.47 times (95% CI, 1.11-1.96) in the AAA group and 1.45 times (95% CI, 1.02-2.07) in the HF group compared to the controls (P=.007 and P=.038, respectively). When comparing AAA and HF group, the difference between the groups was not statistically significant (crude OR 1.16 [95% CI, 0.95-1.41], *P*=.144, and adjusted OR 1.02 [95% CI, 0.73 – 1.44]. P=.895).

Cancer risk by age group

Age-specific cancer risk was analyzed (Table 5). In AAA patients younger than 65 years, the cancer risk was 2.01 times than control group (95% CI, 1.27-3.18, P=.003). Similarly, HF patients younger than 65 years showed 2.20 higher risk than control group (95% CI, 1.40-3.47, P=0.001). In patients equal or older than 65 years, AAA patients had significantly higher risk than control group, while HF patients had similar risk to controls (P=.004 and P=.300, respectively)

Table 4. Comparison of Cancer risk among three groups

		AAA (N=372)	Matched HF (N=343)	Matched Control (N=294)
Crude OR (95% CI)		1.50 (1.23 - 1.83)	1.29 (1.06 - 1.58)	1 (Reference)
	p	<.001	0.012	
		1.16 (0.95 - 1.41)	1 (Reference)	0.77 (0.63-0.95)
	p	0.144		0.012
Adjusted[a] OR (95% CI)		1.52 (1.24 - 1.86)	1.37 (1.09 - 1.72)	1 (Reference)
	p	<.001	0.006	
		1.11 (0.90 - 1.37)	1 (Reference)	0.73 (0.58-0.91)
	p	0.340		0.006
Adjusted[b] OR (95% CI)		1.48 (1.11 – 1.96)	1.45 (1.02 – 2.06)	1 (Reference)
	p	0.007	0.038	
		1.02 (0.72 – 1.42)	1 (Reference)	0.69 (0.49 – 0.98)
	p	0.930		0.038
Adjusted[c] OR (95% CI)		1.47 (1.11 – 1.96)	1.45 (1.02 – 2.07)	1 (Reference)
	p	0.008	0.038	
		1.02 (0.73 – 1.44)	1 (Reference)	0.68 (0.48 – 0.97)
	p	0.895		0.038

AAA, abdominal aortic aneurysm; HF, heart failure

[a] adjusted by hypertension, diabetes, dyslipidemia

[b] adjusted by hypertension, diabetes, dyslipidemia, smoking

[c] adjusted by hypertension, diabetes, dyslipidemia, smoking, alcohol

Table 5. Cancer risk stratified by age group (50-65 and ≥65 years)

		AAA	Matched HF	Matched Control
Age ≥ 50 and < 65 years		n=196	n=196	n=196
Cancer				
No		122 (62.2)	118 (60.2)	149 (76.0)
Yes		74 (37.8)	78 (39.8)	47 (24.0)
Crude OR (95% CI)		2.01 (1.27-3.18)	2.20 (1.40-3.47)	1 (Reference)
	p	0.003	0.001	
Adjusted[a] OR (95% CI)		2.02 (1.28-3.19)	2.27 (1.43-3.60)	1 (Reference)
	p	0.003	0.001	
Adjusted[b] OR (95% CI)		2.43 (1.33-4.42)	2.40 (1.19-4.84)	1 (Reference)
	p	0.004	0.014	
Age ≥ 65 years		n=627	n=627	n=627
Cancer				
No		329 (52.5)	362 (57.7)	380 (60.6)
Yes		298 (47.5)	265 (42.3)	247 (39.4)
Crude OR (95% CI)		1.40 (1.12-1.75)	1.13 (0.90-1.41)	1 (Reference)
	p	0.004	0.300	
Adjusted[a] OR (95% CI)		1.42 (1.13-1.78)	1.17 (0.91-1.49)	1 (Reference)
	p	0.003	0.225	
Adjusted[b] OR (95% CI)		1.28 (0.93-1.76)	1.28 (0.87-1.89)	1 (Reference)
	p	0.137	0.206	

[a] adjusted by hypertension, diabetes, dyslipidemia

[b] adjusted by hypertension, diabetes, dyslipidemia, smoking

3. Risk of new onset cancer

The risk of cancer is described in patients without previous history of cancer or without cancer until 6 months after index date in Table 6.

Table 6. Cancer incidence in subjects without cancer until 6 months after index date

		AAA (n=823)	**Matched HF** (n=823)	**Matched Control** (n=823)
No. of patients without cancer until 6 months after index date		590	708	642
No. of cancer 6 months after the index date		92	199	101
Cancer incidence per 100 person-years		4.36	4.16	3.43
Unadjusted HR (95% CI)		1.30 (0.97 - 1.72)	1.14 (0.90 – 1.46)	1 (Reference)
	p	.075	.285	
		1.15 (0.90 - 1.47)	1 (Reference)	0.87 (0.68-1.10)
	p	.276		.245
Adjusted[a] HR (95% CI)		1.39 (1.04 - 1.47)	1.16 (0.89 - 1.51)	1 (Reference)
	p	.025	.273	
		1.20 (0.93 – 1.55)	1 (Reference)	0.86 (0.66-1.12)
	p	.170		.273
Adjusted[b] HR (95% CI)		1.48 (1.05 - 2.08)	1.23 (0.87 - 1.74)	1 (Reference)
	p	.027	.244	
		1.20 (0.85 – 1.69)	1 (Reference)	0.81 (0.57 - 1.15)
	p	.295		.244
Adjusted[c] HR (95% CI)		1.51 (1.07 - 2.13)	1.26 (0.89 - 1.79)	1 (Reference)
	p	.020	.192	
		1.19 (0.85 - 1.68)	1 (Reference)	0.79 (0.56 - 1.12)
	p	.308		.192

[a] adjusted by age, sex, DM, HTN and dyslipidemia

[b] adjusted by age, sex, DM, HTN, dyslipidemia and smoking

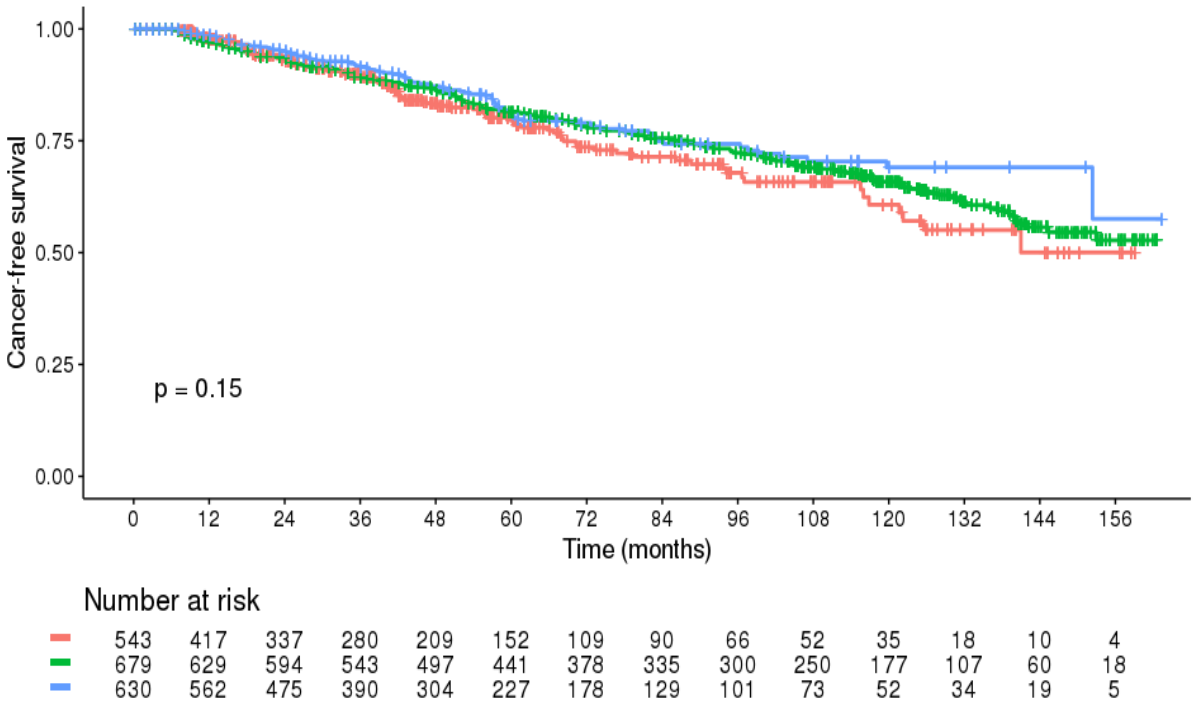
[c] adjusted by age, sex, DM, HTN, dyslipidemia, smoking and alcohol

The cancer development rate per 100 person-years was 6.87 in AAA group, 4.88 in HF group and 3.89 in control group. Unadjusted HR was 1.72 (95% CI, 1.35 - 2.21) for AAA group (P<0.001) and 1.28 (95% CI, 1.02 - 1.60) for HF group (*P*=.035) with compare to the control group. Adjusted HR by age, sex, DM, hypertension and dyslipidemia 0.71 (95%CI, 0.56 - 0.88) for AAA group (*P*=.002) and 0.56 (0.43-0.72) for HF group (*P*<.001) with compare to the control group.

In patients without cancer until 6 months after the index date, the cancer risk was not significantly different between the group (*P* =.199) (Figure 4).

Figure 4. Cancer free survival during the long-term follow-up in patients without cancer until 6 months after index date

(red line: AAA group, green line: HF group, and blue line: controls).



4. Mortality rate and cause of death

Comparison of mortality rate

The mortality rate of each group is summarized in Table 7.

Table 7. Comparison of mortality rate

		AAA	HF	Matched control
Total		823	823	823
No. of death		343	433	170
Mortality rate per 100 person-years		11.11	6.80	4.40
5 year survival rate (%)		57.66 (53.74-61.58)	75.17 (72.21-78.13)	80.87 (77.73-84.01)
Unadjusted HR (95% CI)		2.64 (2.22 - 3.13)	1.63 (1.37 - 1.92)	1 (Reference)
	p	<.001	<.001	
		1.61 (1.42-1.84)	1 (Reference)	0.65 (0.55-0.76)
	p	<.001		<.001
Adjusted[a] HR (95% CI)		2.82 (2.34-3.39)	1.52 (1.25-1.84)	1 (Reference)
	p	<.001	<.001	
		1.86 (1.59-2.17)	1 (Reference)	0.67 (0.54-0.80)
	p	<.001		<.001
Adjusted[b] HR (95% CI)		2.95 (2.30-3.77)	1.51 (1.14-2.01)	1 (Reference)
	p	<.001	0.005	<.001
		1.95 (1.56-2.45)	1 (Reference)	0.66 (0.50-0.88)
		<.001		0.005
Adjusted[c] HR (95% CI)		2.89 (2.25-3.70)	1.50 (1.12-1.99)	1 (Reference)
	p	<.001	0.006	<.001
		1.93 (1.54-2.42)	1 (Reference)	0.67 (0.50-0.89)
		<.001		0.006

[a] adjusted by age, sex, DM, HTN and dyslipidemia

[b] adjusted by age, sex, DM, HTN, dyslipidemia and smoking

[c] adjusted by age, sex, DM, HTN, dyslipidemia, smoking and alcohol

Mortality rate per 100 person years were 11.11 in AAA group, 6.80 in HF group and 4.40 in controls. Patients with AAA had 2.82 times higher mortality risk than controls (P <.001). When compared to the HF group, AAA patients showed higher mortality rate (P<.001). In AAA group, 5-year survival rate was 57.7% (95% CI, 53.7-61.6). Five-year survival rate of HF group and controls were 75.17% (95%CI, 72.2-78.1) and 80.87% (95% CI, 77.7-84.0).

Cause of death

The cause of death is summarized in Table 8. Most common cause of death was cancer and ruptured AAA, followed by cardiovascular and cerebrovascular disease, in AAA group. In HR and control group, most common cause of death was cancer, cardiovascular and cerebrovascular disease. Most common type of cancer related to the death was lung cancer. Prostate cancer was not identifiable with the diagnosis code in the database, but it was listed in the cause of death database. It was second most common cancer as cause of death in AAA and HF group and fourth in controls. Cardiovascular death AAA rupture-related death was detected in 64 (7.8%) patients in AAA group, which was the same frequency as cancer-related death. Cardiovascular death accounted for 3.8% in the AAA group, 5.6% in the HF group, and 1.6% in the control group.

Table 8. Major cause of death

Category of death	AAA	HF	Control	Total
Total number of death	340 (41.3)	431 (52.4)	170 (20.7)	941 (38.1)
Cancer	64 (7.8)	82 (10.0)	45 (5.5)	191 (7.7)
Lung	23 (2.8)	21 (2.6)	11 (1.3)	55 (2.2)
Stomach	4 (0.5)	7 (0.9)	6 (0.7)	17 (0.7)
Prostate	3 (0.4)	10 (1.2)	2 (0.2)	15 (0.6)
Colorectal	5 (0.6)	7 (0.9)	2 (0.2)	14 (0.6)
Hematologic	4 (0.5)	5 (0.6)	3 (0.4)	12 (0.5)
Cardiovascular	31 (3.8)	46 (5.6)	13 (1.6)	90 (3.6)
Cerebrovascular	27 (3.3)	36 (4.4)	10 (1.2)	73 (3.0)
Ruptured AAA	64 (7.8)	0	0	64 (2.6)
COPD	10 (1.2)	29 (3.5)	4 (0.5)	43 (1.7)
Pneumonia	13 (1.6)	17 (2.1)	7 (0.9)	37 (1.5)
Intracranial hemorrhage	8 (1.0)	7 (0.9)	5 (0.6)	20 (0.8)

Each cell is presented by n (%).

AAA, Abdominal aortic aneurysm; HF, Heart failure; COPD, Chronic obstructive pulmonary disease

Mortality rate with and without cancer in AAA patients.

Table 9 summarizes the difference in mortality rate according to cancer in AAA patients. There was no statistically significant difference in the mortality rate in patients with cancer in AAA group when compared to that in patients without cancer (unadjusted HR, 1.13 [95% CI, 0.91-1.40], P=.263; adjusted HR, 1.02 [0.77 – 1.36], *P* =.871).

Table 9. Mortality rate according to cancer in AAA patients.

	AAA		
	Total	**Without cancer**	**With cancer**
Total	823	451	372
No. of death	343	175	168
Death rate per 100 person-years	11.11	10.51	11.81
5-year survival rate (%)	57.66 (53.74-61.58)	61.48 (56.34-66.62)	53.38 (47.44-59.32)
Unadjusted HR (95% CI)		1 (Reference)	1.13 (0.91-1.40)
p			0.263
Adjusted[a] HR (95% CI)		1 (Reference)	1.02 (0.82-1.27)
p			0.833
Adjusted[c] HR (95% CI)		1 (Reference)	1.02 (0.77-1.36)
p			0.871

[a] adjusted by age, sex, DM, HTN and dyslipidemia

[b] adjusted by age, sex, DM, HTN, dyslipidemia and smoking

Discussion

The present study purposed to evaluate the possible association between abdominal aortic aneurysm and cancer. In this study, we analyzed each 823 of AAA patients, HF patients and controls. The association between AAA and cancer has been suggested in the previous studies, but it was difficult to clarify because it was difficult to obtain enough number of patients that have sufficient power. To our best knowledge, this study is one of the first publications with a large, validated sample cohort of patients with AAA demonstrating the risk of cancer through comparison with HF group well known for high cancer risk as well as control group without AAA. The NHIS-NSC is a representative database constructed by systematic stratified random sampling with proportional allocation within each stratum according to the individual's total annual medical expenses.[29] Especially, ICD-10 code for cancer is validated in its accuracy by comparison of Korea National Cancer Incidence Database

built by the Korea Central Registry, which registers biopsy-proven malignancies only.[30] Moreover, to maximize accuracy of the cancer patients selection, we defined patients with cancer as those who visited outpatient clinic at least twice in a year with the same code. The reason HF was selected as the control group was that there were many previous reports suggesting association with cancer in the heart failure group.[27,28,31,32] In our study, the risk of cancer in AAA patients were highest among three groups (45.2% for AAA group vs 41.7% for HF group vs 35.7% for control). Especially, the AAA group showed significantly higher cancer risk, which was 1.52 times higher than that of the control group. When compared to HF group, the risk was similar (crude OR 1.11, P=0.340). Therefore, the finding from this study is not only occasional or related to the age of patients but it appears there is strong association between AAA and cancer.

Our data support previous reports on higher prevalence of cancer in AAA patients.[33,34] AAA and cancer overlap at multiple levels, which has raised the question of whether this is a simple collision, association or causation. Cancer was diagnosed in more cases before AAA detection than after. Total 372 of cancer patients, 139 developed after the diagnosis of the AAA and 233 patients were diagnosed with cancer prior to the AAA diagnosis. Therefore, in present study, temporal relationship between AAA and cancer did not appear unidirectional. Moreover, since both diseases progress slowly and the order of discovery does not mean the order of onset, it is difficult to conclude which disease precedes to other. One notable thing is, however, that our study showed that coexistence of the two diseases is not a mere coincidence, but a strong relationship. Although we could not hypothesize the relationship between two diseases due to the nature of data that do not provide detailed medical history, it seems reasonable to see that there is an association rather than a causation intuitively. Looking at the temporal sequence of AAA, HF, and cancer in our study, AAA has a high pre-diagnosis cancer risk, whereas HF has an increased post-diagnosis cancer risk. The risk of newly developed cancer was rather lower in AAA than control when adjusted by underlying risk factors, which suggests that the risk of developing cancer is higher before the diagnosis of AAA. Therefore, it is presumed that there was a tendency that HF occurred first, followed by cancer, then AAA.

Suggested mechanisms of coexistence of the AAA and malignancies includes common risk factor. Like other cardiovascular diseases, AAA shares a number of modifiable risk factors with cancer, and often coexist in the same individuals.[35] Smoking as one of the most important causes of AAA can stimulate abnormal signaling pathways that leads to be involved in the pathogenesis of both AAA and lung cancer.[8,16] Another mechanism is disturbed interaction between matrix proteins and epithelial cells which facilitate angiogenesis or carcinoma and the aneurysm prone phenotype.[33,36] It is also suggested that it might be due to the presence of chronic inflammatory cells and cytokines in AAA patients as well as their angiogenesis status.[35] Similar findings were observed in epidemiologic studies on cardiovascular diseases with a higher incidence of cancer[37,38], as well as the experimental studies.[31] Systemic pathological processes, such as inflammation and oxidative stress is one of the main hypotheses, possibly superimposed on a background of genetic predisposition.[39] Circulating neurohormonal factors have also been shown to affect tumor biology.[31] On the other hand, cardiovascular diseases, especially heart failure, have been studied for correlation with cancer. Cardiovascular disease is an important cause of death for many cancer survivors and rivals cancer recurrence.[40] This tendency may be related to the cardiovascular toxicity of chemotherapeutic agents or radiation, shared cardiovascular risk factors, and common pathogenesis of both diseases.[41] Previous registry-based cohorts of myocardial infarction patients showed a modest 5–8% increased risk of cancer.[42-44] Likewise, the incidence of cancer was increased among patients with preexisting HF, with the estimated incidence in the range of 18.9-33.7 per 1000 person-years.[37,45-47] Increased age in these population, shared risk factors and surveillance during active follow-up may result in growing prevalence of coexistence.[37,48] However, recent evidence with experimental models suggested that several pathophysiologic mechanisms are involved between the two diseases. First, systemic inflammation and oxidative stress were suggested as biological mechanism.[35] HF with reduced ejection fraction induces hyperactivation of progressive neurohormonal axes; sympathetic nervous system (SNS) and renin-angiotensin-aldosterone system (RAAS), and this hallmark of HF may affect tumor biology.[41] SNS may affect carcinogenesis through several mechanisms; resistance to apoptosis, tumor spread by upregulating matric metalloprotease (MMP)-2 and MMP-9 via β-AR signalling[49,50].

The RAAS effects oncogenesis with paracrine and autocrine functions and the expression of type 1 angiotensin receptor is related to tumor growth and invasion and vascularization.[51] As shown in this study, cancer risk in AAA patients was higher than in the HF group and increased risk of cancer was more apparent in particularly younger patients with AAA than the control group. More research will be warranted to delineate association between AAA and cancer.

In our study, the mortality rate was 2.64 times higher than controls in AAA group (p<.001). However, when adjusted by age, sex, and underlying diseases, mortality risk was lower than controls (adjusted HR 0.51 (95%CI, 0.41-0.65). This finding suggested that it is not AAA itself but associated risk factors substantially increase the mortality rate. Most common cause of death in AAA patients was cancer, followed by ruptured AAA and cardiovascular disease. Although declining gradually over time, a substantial mortality risk is associated with ruptured AAA,[52,53] and similar findings were observed in our study. As indicated by our study, cancer risk was significantly higher in AAA group. Therefore, it is necessary to run effective screening programs for these diseases in those at highest risk, because both AAA and cancer possess significant mortality if they go unnoticed [16].

However, preventive efforts in cardiology and oncology have long been disconnected from each other.[54] We believe our study can stimulate further research to delineate connection between AAA and cancer and to shed light on possible mechanisms and risk factors, and eventually to develop cost-effective and practical surveillance protocol.

Limitation

This study has several limitations. First. The national database may include some misclassification of the diagnosis. To get the most accurate target patients possible, we pre-evaluated hospital data and included accurate diagnostic codes only to our analysis. In addition, we excluded AAA related to the distinct mechanism such as infection or Behcet's disease from the study. Second, this claim data offers limited clinical data including smoking history because only patients who have undergone national health check-up obtain information. As a result, it was not possible to hypothesize some potential mechanisms on the association between AAA and cancer. Third, we tried to eliminate infective AAA but diseases related to typhoid fever and syphilis is masked from the database by

categorized into sensitive diagnosis related to the personal privacy. As the number of Behcet's disease patients was as few as 11, it was assumed to be a negligible number. Despite these limitations, current study has strengths. First, it is the largest study investigating association in patients with AAA and cancer considering that it is relatively infrequent that both of AAA and cancer coexist in one patient. Moreover, we matched AAA patients to HF patients whose association with cancer is already suggested as well as control group, supporting our findings.

Conclusion

There was significantly higher prevalence of cancer in AAA group than HF group or controls and increased risk of cancer over time during the 13 years of follow-up. Further research is needed to validate possible shared pathologic process. In the meantime, effective screening program for both diseases need to be developed.

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국문초록

배경: 암과 복부대동맥류는 사망률과 이환율이 높은 질환이며 두 질환 모두 고령에서 발생율이 높다 두 질환이 공존하는 경우 치료에 어려움이 있고 생존율이 낮은 것으로 알려져 있다. 두 질환이 공존하는 경우는 비교적 흔하지 않기 때문에 두 질환의 상관관계는 아직까지 분명하지 않은 상태이다. 이 연구에서는 국민건강보험공단 자료를 이용한 분석을 통하여 두 질환의 상관관계를 밝히고자 한다.

방법: 국민건강보험공단 표본코호트를 이용하여 연구를 시행하였다. 대상자는 2002 년부터 2015 년 사이 50 세 이상으로 하였고 복부대동맥류와 관련한 ICD-10 코드를 이용하여 선정하였다. 대조군으로 복부대동맥류가 없는 심부전환자와 두 군을 뺀 나머지 환자를 성별, 나이, 심혈관질환 위험인자로 1:1:1 짝짓기를 시행하였다. 주요 관심 결과는 복부대동맥류 유무에 따른 암발생율의 차이이며 부수적으로 암 여부에 따른 생존율 분석과 암 발생 위험도를 분석하였다.

결과: 포함기준을 만족시키는 환자는 총 823 명으로 평균 나이는 71.8 세 (표준편차 9.4), 그중 67.1 % (552/823)는 남자였다. 비교를 위해 대조군으로 각각 823 명의 심부전환자와 823 명의 환자를 선정하였다. 각 군에서 암이 동반된 환자는 복부대동맥류 환자군에서 372 명 (45.2%), 심부전군에서 343 명 (41.7%), 대조군에서 294(35.7%) 명으로 암유병율은 대조군에 비해 유의하게 높았다 (P<.001). 암발생 시기는 복부대동맥류 진단 6 개월 이전에서 177 명 (21.5%), 복부대동맥류 진단 6 개월 이전에서 6 개월 이후 사이에 103 명 (12.5%), 복부대동맥류 발생 6 개월 이후에 암이 발생한 경우는 92 명 (11.2%)였다. 암발생 위험도는 복부대동맥류 환자에서 심부전군과 마찬가지로 대조군에 비해 유의하게 높았다(복부대동맥류 환자의 보정 위험비, 1.52 [95% 신뢰구간, 1.24 – 1.86]: P<.001, 심부전 환자의 보정 위험비, 1.37 [95% 신뢰구간, 1.09 – 1.72]: P=.006). 100 인년당 암 연관 사망률은 복부대동맥류군에서 4.36, 심부전군에서 4.16, 대조군에서 3.43 으로 복부대동맥류군에서는 대조군에 비해 2.64 배 높았고 ([95% 신뢰구간, 2.22-3.13], P<001) 심부전환자군에서는 대조군에 비해 1.63 배

높았다 ([95% 신뢰구간, 1.37-1.92], P<.001). 복부대동맥류 환자에서 장기 관찰 중 주요 사인은 암, 심혈관질환, 뇌혈관질환이었다.

결론: 복부대동맥류 환자에서 암 발생율 및 암 발생위험도는 대조군 및 심부전증 환자군에 비해 유의하게 높았다. 복부대동맥류 환자에서의 가장 흔한 사인은 암과 심혈관계질환이었다. 따라서 복부대동맥류와 암을 동시에 조기 발견할 수 있는 적절한 선별검사가 필요하다.

주요어: 복부대동맥류; 악성신생물; 사망률; 사인; 심부전

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