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Risk and predictors of subsequent cancers of patients with newly-diagnosed atrial fibrillation — A nationwide population-based study

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Aims: Patients with atrial fibrillation (AF) may be at higher risk for cancer, possibly due to the presence of coexisting risk factors. In this study, we investigate the magnitude and predictors of this potential risk within a population-based study.
Methods and results: The study cohort included 332,555 AF patients aged ≥20 years without past history of cancer. Standardized incidence ratio (SIR) was used as a measure of relative risk, comparing observed cancer incidence among patients with AF with that expected based on cancer incidence in the Taiwanese population. During the observation period, 22,911 incident cancers occurred with an incidence of 1.65%/year. Compared with the general population, AF patients had a significantly higher cancer risk with a SIR of 1.37 (95%CI = 1.36–1.39). Patients with new-onset AF had an elevated cancer risk which was highest within 1 year (SIR = 2.30; 95%CI, 2.25–2.36) and persisted beyond 10 years after AF was diagnosed (SIR = 1.18; 95%CI, 1.11–1.25). Age ≥ 65 years, male gender, hypertension, diabetes, chronic obstructive pulmonary disease (COPD) and liver cirrhosis were significantly associated with development of cancers among AF patients. The hazard ratio of cancers increased from 1.40 (95%CI = 1.28–1.53) for patients having 1 risk factor to 5.14 (95%CI = 4.03–6.06) for patients with 6 risk factors, in comparison to those without any risk factors.
Conclusion: In the nationwide cohort study, we show that AF patients had a higher risk of cancer. Age, male gender, hypertension, diabetes, COPD and liver cirrhosis are important risk factors of cancer among AF patients. Prompt and detailed examinations may be considered for incident AF patients with multiple risk factors to early detect the occult malignancy.

1. Background

Atrial fibrillation (AF) is a disease of the elderly, with an increasing prevalence and incidence with age. AF not only increases the risk of stroke, but also increased the risk of death by 1.5 fold in males and 1.9-fold in females in the Framingham Heart Study [1].

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Although cardiovascular diseases represented the most common cause of mortality among AF patients, cancer also accounted for approximately 11% of all deaths in patients with AF in a recent pooled analysis of 4 randomized trials of non-vitamin K antagonist oral anticoagulants (NOACs) versus warfarin [2]. In GARFIELD-AF registry, cancer-related mortality was consistently responsible for 11.1% and 10.3% of all deaths at 1 year and 2 years after incident AF, respectively [3,4]. Given the increasing occurrence of cancer in the elderly and the coexistence of risk factors predisposing to both AF and cancer, a close association between these 2 conditions is possible [5,6]. In a recent study, which followed 34,691 initially healthy females for a median of 19.1 years, women with new-onset AF had an elevated cancer risk that was highest within 3 months and even persisted beyond 1 year of AF diagnosis [7]. Several previous small studies have also reported significant association between cancer subtypes and AF [8–10]. Population-based estimates are sparse, with the notable exception of a Danish study that found an increased relative risk of cancer within three months of AF diagnosis in 269,742 AF patients over 3.4 years of follow-up [11]. However, the detailed analysis regarding the predictors of cancer among AF patients was not performed, and therefore, how to identify AF patients with a high risk of cancer remains unknown.

In the present study, we aimed to investigate the absolute and relative risk of cancer after AF was diagnosed, and further aimed to identify populations of AF patients at higher cancer risk.

2. Methods

The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

2.1. Database

This study used the "National Health Insurance Research Database (NHIRD)" released by the Taiwan National Health Research Institutes (NHRI). The National Health Insurance (NHI) system is a mandatory universal health insurance program that offers comprehensive medical care coverage to all Taiwanese residents. NHIRD consists of detailed health care data from >23 million enrollees, representing >99% of Taiwan's population. In this cohort dataset, the patients' original identification numbers have been encrypted to protect their privacy, but the encrypting procedure was consistent, so that the claims belonging to the same patient can be linked within the NHI database, which is continuously updated. The large sample size of this database provided a good opportunity to study the risk of cancer among AF patients and its predictors.

2.2. Study population

The study protocol of the present study was similar to our previous studies [12–19]. From January 1, 1996 to December 31, 2011, a total of 354,649 AF patients aged ≥20 years were identified from the NHIRD, and 332,555 patients without past history of cancer were selected as the study population. AF was diagnosed using the International Classification of Diseases (ICD), Ninth Revision, Clinical Modification (ICD-9-CM) codes (427.31) registered by the physicians responsible for the treatments of patients. To ensure the accuracy of diagnosis, we defined patients with AF only when it was a discharge diagnosis or confirmed for at least 2 times in the outpatient department. The positive predictive value of AF using this definition in NHIRD has been reported to be nearly 90% [20].

The comorbidities of each subject were identified according to the ICD-9-CM codes registered by clinical physicians responsible for the care of the patient. Insurance premiums, calculated according to the beneficiary's total income, were used to estimate monthly income. Monthly income was grouped into low income (monthly income <20,000 New Taiwan Dollar [NTD]), medium income (20,000 NTD ≤ monthly income <40,000 NTD), and high income (monthly income ≥40,000 NTD). Information about the degree of urbanization (urban, suburban or rural) of each patient was available in Taiwan NHIRD based on the townships where the patients lived. The stratifications of townships were based on the township population density (people/km2), population ratio of people with college or above educational levels, population ratio of elder people over 65 years old, population ratio of people of agriculture workers and the number of physicians per 100,000 people. The occurrence of cancer was diagnosed by both specific ICD-9-CM codes and inclusion in the Registry for Catastrophic Illness Patient Database (RCIPD), a subpart of the NHIRD. Those patients who meet the criteria of "catastrophic illness" have copayment exemptions under the NHI program, and all malignancies are categorized as catastrophic illnesses according to the rules of Taiwan NHI system.

2.3. Relative risk of cancer of AF patients

We used standardized incidence ratio (SIR) as a measure of relative risk, comparing the cancer incidence observed among AF patients with that expected in the Taiwanese population [21]. SIR is defined as the observed number of cancer occurrences divided by the expected number, to determine the risk of cancer among AF patients. To count the expected numbers of cancers, the cancer incidence rate in the general population is multiplied by age, sex and calendar year in five-year intervals by the corresponding stratum-specific person-time accrued in the cohort. The cancer incidence rate among the general population was obtained from Taiwan's National Cancer Registry. According to the assumption that the observed numbers of cancers followed a Poisson probability distribution, the 95% confidence intervals (CIs) of the SIRs were estimated. The SIRs for different types of cancers and among subgroups based on age, sex and comorbidities of patients were estimated. In addition, the SIRs were calculated in different time periods after AF was diagnosed.

2.4. Statistical analysis

Data were presented as the mean value and standard deviation (SD) for continuous variables, and proportions for categorical variables. Differences between continuous values and nominal variables were assessed using the unpaired two-tailed *t*-test and chi-squared test, respectively. Incidence rates of cancer of AF patients were calculated by dividing the number of events by person-time at risk, with the 95% CI estimated by exact Poisson distribution. By using univariate and multivariate Cox proportional hazards models, we analyzed the risk factors for developing cancers among AF patients. The cumulative incidence curves of incident cancers for AF patients with different numbers of risk factors were plotted via the Kaplan-Meier method, with statistical significance examined by the log-rank test. Risk of all statistical significances were set at a $p < 0.05$.

3. Results

The baseline characteristics of study population are shown in Table 1. The mean age of AF patients was 70.8 ± 13.1 years, and 55.2% were men. Hypertension is the most common comorbidity which is prevalent among 68.5% of patients. Overall, the cohort was observed for 1385,140 person-years with a median follow-up of 3.1 years.

3.1. Risk of cancer for AF patients

During the observation period, 22,911 incident cancers occurred with an incidence of 1.65%/year (1.92%/year for males and 1.31%/year for females) in patients with AF. Supplemental Table 1 shows the incidence of cancer among AF patients stratified by different age groups and durations after AF being diagnosed. As expected, the risk of cancer was higher among the elderly compared to younger patients (age ≥ 80 years versus 20–39 years = 2.32%/year versus 0.23%/year; incidence risk ratio [IRR] = 10.29). A peak on the incidence of cancer (event number = 7413; 2.65%/year) was noted within 1 year after AF was diagnosed with an IRR of 10.20 (95% CI = 9.57–10.89) compared to the timing period when AF was diagnosed ≥10 years (event number = 1072; 0.26%/year).

3.2. Relative risk of cancer for AF patients compared to the general population

Compared with the general population, AF patients had a significantly higher overall risk of cancer with a SIR of 1.37 (95% CI = 1.36–1.39) for all patients, 1.37 (95%CI = 1.35–1.40) for males and 1.37 (95%CI = 1.34–1.40) for females (Table 2). The relative risk of cancer was consistently higher for AF patients across all age strata, with the greatest magnitude elevations in risk observed among the youngest patients (Table 2). The relative risk was also similarly elevated across subgroups based on comorbidities (Supplemental Fig. 1). The magnitude of the cancer risk elevation was highest within one year of AF diagnosis (SIR 2.30; 95% CI, 2.25–2.36) but also persisted beyond 10 years after AF was diagnosed (Table 2). The flow chart of patient enrollment, annual risks of incident cancers and SIRs in different timing intervals after AF being diagnosed are summarized in Supplemental Fig. 2.

Table 1
Baseline characteristics of AF patients without a prior history of cancer.

	Total	Male	Female
No. of patients	332,555	183,562	148,993
Age (years), mean (SD)	70.8 ± 13.1	69.4 ± 13.3	72.6 ± 12.8
Age at diagnosis of AF, n(%)			
20–29 years	2174 (0.7)	1446 (0.8)	728 (0.5)
30–39 years	5709 (1.7)	3782 (2.1)	1927 (1.3)
40–49 years	16,964 (5.1)	11,025 (6)	5939 (4.0)
50–59 years	36,812 (11.1)	22,999 (12.5)	13,813 (9.3)
60–69 years	67,834 (20.4)	39,177 (21.3)	28,657 (19.2)
70–79 years	112,684 (33.9)	62,742 (34.2)	49,942 (33.5)
≥80 years	90,378 (27.2)	42,391 (23.1)	47,987 (32.2)
Comorbidities, n(%)			
Hypertension	227,956 (68.5)	121,279 (66.1)	106,677 (71.6)
Diabetes mellitus	94,515 (28.4)	47,073 (25.6)	47,442 (31.8)
Heart failure	136,745 (41.1)	69,548 (37.9)	67,197 (45.1)
History of ischemic stroke	116,068 (34.9)	61,638 (33.6)	54,430 (36.5)
Peripheral arterial disease	28,067 (8.4)	14,671 (8.0)	13,396 (9.0)
Coronary artery disease	8205 (2.5)	5032 (2.8)	3113 (2.1)
Prior MI	25,141 (7.6)	15,940 (8.7)	9201 (6.2)
Aortic aneurysm	1901 (0.6)	1252 (0.7)	649 (0.4)
Aortic dissection	1181 (0.4)	739 (0.4)	442 (0.3)
ESRD	24,751 (7.4)	13,716 (7.5)	11,035 (7.4)
COPD	117,248 (35.3)	72,199 (39.3)	45,049 (30.2)
Liver cirrhosis	10,236 (3.1)	6698 (3.6)	3538 (2.4)
Autoimmune diseases	18,305 (5.5)	7818 (4.3)	10,487 (7.0)
Dyslipidemia	83,207 (25.0)	42,273 (23.0)	40,934 (27.5)
Degree of urbanization, n (%)			
Urban	170,832 (51.4)	96,072 (52.3)	74,760 (50.2)
Suburban	110,836 (33.3)	61,478 (33.5)	49,358 (33.1)
Rural	50,887 (15.3)	26,012 (14.2)	24,875 (16.7)
Income level, n(%)			
Low	177,871 (53.5)	103,604 (56.4)	74,267 (49.8)
Median	111,029 (33.4)	55,973 (30.5)	55,053 (37.0)
High	43,655 (13.1)	23,982 (13.1)	19,673 (13.2)
Person-years at risk	1,385,140	770,567	614,573
Median follow-up, years (interquartile range)	3.10 (0.97–6.53)	3.14 (0.99–6.58)	3.06 (0.94–6.47)

COPD = chronic obstructive pulmonary disease; ESRD = end-stage renal disease; MI = myocardial infarction; SD = standard deviation.

Supplemental Fig. 3 shows the SIRs for AF and main cancer types. The observed risk of cancer for AF patients was consistently higher for all systems, except for the risk of breast cancer for AF males (SIR = 0.62, 95% CI = 0.27–1.23). The detailed results of SIRs in specific types of cancers are shown in Table 3. Generally, AF patients had a higher risk of all types of cancers except for ovarian cancer, breast cancer for males, and Hodgkin's disease for females.

Supplemental Table 2 shows numbers of mortality and durations to mortality after cancer being diagnosed. Around 53.3% of patients suffering from mortalities after cancer being diagnosed and the mean durations from incident cancers to mortalities were 1.23 (SD 1.82) years.

3.3. Predictors of cancer among AF patients

The clinical characteristics of AF patients with or without cancer are shown in Supplemental Table 3. In multivariable Cox regression analysis, six clinical factors (age ≥ 65 years, male gender, hypertension, diabetes, chronic obstructive pulmonary disease and liver cirrhosis) were significantly associated with incident cancer in AF patients (Supplemental Table 4). For 10,236 patients with liver cirrhosis, 1825 (17.8%) of them were alcoholic liver cirrhosis, 1248 (12.2%) were carriers of viral hepatitis B and 1665 (16.3%) were carriers of viral hepatitis C. Chronic obstructive pulmonary disease was not only associated with an increasing risk of lung and mediastinum cancers (HR 1.45, 95%CI 1.36–1.55), but also those other than lung and mediastinum (HR 1.26, 95%CI 1.22–1.30).

The incidence of cancer increased from 0.70%/year for patients without any risk factors to 2.76%/year for those with 6 risk factors (Fig. 1). Although lower, the incidence of cancer in AF patients without risk factors remained elevated as compared to the general population (IRR of 1.30; 95%, 1.20–1.40). The relative risk of cancer among AF patients was proportional to the number of risk factors attributable to a patient, where the HR of cancers increased from 1.40 (95%CI = 1.28–1.53) for 1 risk factor rising to 5.14 (95% CI = 4.03–6.06) for patients with 6 risk factors, in comparison to those without any risk factors. With an increase in the number of risk factors in AF patients, the cumulative event rate correspondingly increased (Supplemental Fig. 4).

4. Discussion

4.1. Main findings

To our knowledge, this is the largest observational cohort of AF patients in which the absolute and relative risk of cancer and its predictors were investigated. Our principal findings are as follows:

Table 2
Standardized cancer incidence ratios stratified by sex, age at diagnosis of AF and durations after AF being diagnosed.

Characteristics	All			Male			Female		
	Observed	Expected	SIR (95% CI)	Observed	Expected	SIR (95% CI)	Observed	Expected	SIR (95% CI)
All cancers	22,911	16,666.99	1.37 (1.36–1.39)	14,828	10,784.34	1.37 (1.35–1.40)	8083	5882.63	1.37 (1.34–1.40)
Age at diagnosis of AF									
20–39 years	56	29.16	1.92 (1.45–2.49)	32	16.83	1.90 (1.30–2.68)	24	12.33	1.95 (1.25–2.90)
40–59 years	1765	1113.49	1.59 (1.51–1.66)	1138	713.82	1.59 (1.50–1.69)	627	399.67	1.57 (1.45–1.70)
60–79 years	13,318	9649.92	1.38 (1.36–1.40)	8957	6515.81	1.37 (1.35–1.40)	4361	3134.09	1.39 (1.35–1.43)
≥ 80 years	7772	5874.42	1.32 (1.29–1.35)	4701	3537.88	1.33 (1.29–1.37)	3071	2336.54	1.31 (1.27–1.36)
Durations after AF being diagnosed									
0–1, years	7413	3216.15	2.30 (2.25–2.36)	4722	2045.09	2.31 (2.24–2.38)	2691	1171.06	2.30 (2.21–2.39)
1–5, years	9568	8224.49	1.16 (1.14–1.19)	6170	5294.79	1.17 (1.14–1.19)	3398	2929.70	1.16 (1.12–1.20)
5–10, years	4858	4314.74	1.13 (1.09–1.16)	3198	2835.68	1.13 (1.09–1.17)	1660	1479.06	1.12 (1.07–1.18)
≥10, years	1072	911.60	1.18 (1.11–1.25)	738	608.78	1.21 (1.13–1.30)	334	302.81	1.10 (0.99–1.23)

AF = atrial fibrillation; CI = confidence interval; SIR = standardized incidence ratio.

Table 3
Standardized incidence ratios (SIRs) for specific cancer types among patients with AF.

Site of cancers	All			Male			Female		
	Observed	Expected	SIR (95% CI)	Observed	Expected	SIR (95% CI)	Observed	Expected	SIR (95% CI)
All cancers	22,911	16,666.98	1.37 (1.36–1.39)	14,828	10,784.35	1.37 (1.35–1.40)	8083	5882.63	1.37 (1.34–1.40)
Head and neck	1100	939.52	1.17 (1.10–1.24)	936	803.87	1.16 (1.09–1.24)	164	135.65	1.21 (1.03–1.41)
Digestive system	10,099	7197.77	1.40 (1.38–1.43)	6511	4665.27	1.40 (1.36–1.43)	3588	2532.50	1.42 (1.37–1.46)
Esophagus	487	307.78	1.58 (1.44–1.73)	430	270.73	1.59 (1.44–1.75)	57	37.05	1.54 (1.17–1.99)
Stomach	1579	1142.07	1.38 (1.32–1.45)	1068	786.80	1.36 (1.28–1.44)	511	355.27	1.44 (1.32–1.57)
Colon and rectum, anus	4116	2882.31	1.43 (1.38–1.47)	2507	1744.63	1.44 (1.38–1.49)	1609	1137.68	1.41 (1.35–1.49)
Liver and biliary tract	3449	2495.68	1.38 (1.34–1.43)	2231	1648.57	1.35 (1.30–1.41)	1218	847.11	1.44 (1.36–1.52)
Pancreas	468	369.93	1.27 (1.15–1.39)	275	214.54	1.28 (1.13–1.44)	193	155.39	1.24 (1.07–1.43)
Lung and mediastinum	4010	2650.15	1.51 (1.47–1.56)	2836	1888.63	1.50 (1.45–1.56)	1174	761.52	1.54 (1.45–1.63)
Bone and soft tissue	160	116.61	1.37 (1.17–1.60)	106	76.43	1.39 (1.14–1.68)	54	40.18	1.34 (1.01–1.75)
Skin	557	452.32	1.23 (1.13–1.34)	311	235.15	1.32 (1.18–1.48)	246	217.17	1.13 (1.00–1.28)
Breast	808	662.00	1.22 (1.14–1.31)	8	12.84	0.62 (0.27–1.23)*	800	649.16	1.23 (1.15–1.32)
Genitourinary system	3939	3157.80	1.25 (1.21–1.29)	2779	2225.24	1.25 (1.20–1.30)	1160	932.56	1.24 (1.17–1.32)
Cervix	380	341.24	1.11 (1.00–1.23)	N/A	N/A	N/A	380	341.24	1.11 (1.00–1.23)
Uterus	119	90.33	1.32 (1.09–1.58)	N/A	N/A	N/A	119	90.33	1.32 (1.09–1.58)
Ovaries	106	91.32	1.16 (0.95–1.40)*	N/A	N/A	N/A	106	91.32	1.16 (0.95–1.40)*
Prostate	1775	1413.09	1.26 (1.20–1.32)	1775	1413.09	1.26 (1.20–1.32)	N/A	N/A	N/A
Bladder	917	745.08	1.23 (1.15–1.31)	670	554.26	1.21 (1.12–1.30)	247	190.81	1.29 (1.14–1.47)
Kidneys	642	476.74	1.35 (1.24–1.45)	334	257.89	1.30 (1.16–1.44)	308	218.85	1.41 (1.25–1.57)
Thyroid	227	126.04	1.80 (1.57–2.05)	87	41.63	2.09 (1.67–2.58)	140	84.41	1.66 (1.40–1.96)
Hematologically related	1125	734.35	1.53 (1.44–1.62)	741	472.25	1.57 (1.46–1.69)	384	262.10	1.47 (1.32–1.62)
Non-Hodgkin's lymphoma	530	366.34	1.45 (1.33–1.58)	343	231.06	1.48 (1.33–1.65)	187	135.28	1.38 (1.19–1.60)
Hodgkin's disease	15	10.20	1.47 (0.82–2.42)*	14	7.49	1.87 (1.02–3.14)	1	2.72	0.37 (0.01–2.05)*
Multiple myeloma	211	113.55	1.86 (1.62–2.13)	140	72.91	1.92 (1.62–2.27)	71	40.64	1.75 (1.36–2.20)
Leukemia	369	244.25	1.51 (1.36–1.67)	244	160.79	1.52 (1.33–1.72)	125	83.46	1.50 (1.25–1.78)
All others	886	630.42	1.41 (1.31–1.50)	513	363.04	1.41 (1.29–1.54)	373	267.38	1.40 (1.26–1.54)

AF = atrial fibrillation; CI = confidence interval; SIR = standardized incidence ratio.
* P value >0.05.

(i) AF patients had an increased risk of almost every kind of cancer, which was consistently observed in males and females; (ii) the increased risk of cancer was highest within 1 year and persisted beyond 10 years after AF was diagnosed; and (iii) several clinical factors were identified to be significant risk factors of incident cancers for AF patients, including age ≥ 65 years, male gender, hypertension, diabetes, chronic obstructive pulmonary diseases and liver cirrhosis.

4.2. Increased risk of cancer in AF

Few prospective studies have examined the association between AF and cancer. Utilizing a comparable methodology to the present study, Ostendfeld et al. reported a similar elevation in the overall incidence of cancer among AF patients enrolled in a Danish Registry compared to that expected based upon national cancer incidence (SIR 1.31; 95% CI, 1.30–1.33). In this study, elevations in cancer incidence were highest in the 3 months following AF diagnosis; whereas, more modest elevations were observed beyond 3 months of follow-up (SIR 1.13; 95% CI, 1.12–1.15) [11]. In the prospective Women's Health Study, Conen et al. also found that women who developed incident AF had an increased risk of cancer as compared to women without AF over 19 years of follow-up after controlling for potential confounders (HR 1.48, $p < 0.001$). Similar to the Danish registry, the relative risk of cancer was highest in the first 3 months after new-onset AF (HR = 3.54), but the risk remained significantly elevated even beyond 1 year (HR = 1.42) [5]. Similar to these previous studies, we demonstrated that the risk of incident cancer was highest within the initial period (1 year) after new-onset AF (SIR = 2.30), and the increased risk persisted for even >10 years (SIR = 1.18). In our study, we found that the absolute incidence rate of cancer within the first year of AF diagnosis was 2.65 per 100 person-years. Although surveillance and detection biases due to increased contact with the medical system after AF diagnosis may be a possible explanation for a portion of the increased risk of cancer after newly diagnosed AF, these potential biases likely do not fully explain the residual elevations in cancer risk observed among those in whom AF was diagnosed many years prior to cancer

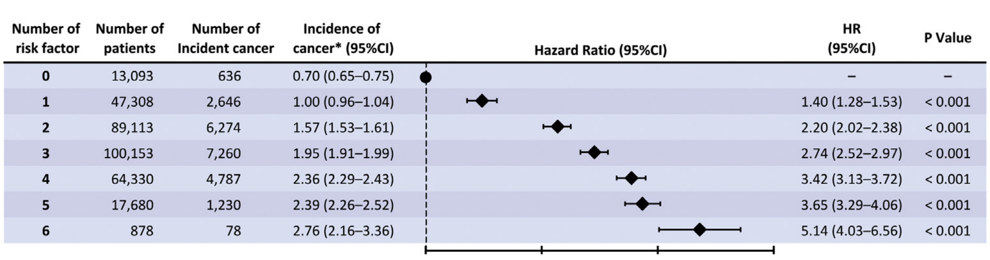

Fig. 1. Risk of cancer in AF patients stratified based on the number of risk factors. The incidence of cancer increased from 0.70%/year for patients without any risk factors to 2.76%/year for those with 6 risk factors. The risk of cancer was proportional to the number of risk factors attributable to a patient, where the HR of cancers increased from 1.40 for 1 risk factor rising to 5.14 for patients with 6 risk factors, in comparison to those without any risk factors. AF = atrial fibrillation; CI = confidence interval. *Number of cancer per 100 person-years of follow up.

diagnosis. Also, we found elevations in cancer risk even among AF patients with established comorbidities that would already be expected to have frequent contact with medical care, and risk elevations were highest among younger patients where no cancer screening is routinely performed. The findings of the previous studies mentioned above together with ours suggest that the physicians should be aware of the possibility of occult cancer in AF patients.

In addition to the surveillance and detection biases, there are other mechanisms that may underlie part of the increased risk of cancer observed in patients with AF. First, systemic inflammation and oxidative stress, which play an important role in the pathogenesis of AF [22–24], are also highly associated with cancer development [25,26]. Second, medications prescribed for AF may contribute to the occurrence of cancer. For example, the amiodarone, which is commonly used for AF patients, has been reported to be associated with an increased risk of cancer [27]. Indeed, in our present study, an especially higher risk of cancer for AF patients was observed at the thyroid (SIR = 1.80), the organ which is more vulnerable to amiodarone. Third, AF patients may share some common risk factors with subsequent cancers, such as diabetes, smoking and alcohol. Further investigation is warranted to determine and clarify the causal relationship between AF and caner, also to disclose the precise mechanisms behind the link.

4.3. Risk factors of cancer in AF

Although the increased risk of cancer among AF patients has been observed, the risk factors of the cancer development among AF patients have not been well studied before. In the present study, we identified several clinical factors associated with an increased risk of cancer for AF patients, including age $\geq$ 65 years, male gender, hypertension, diabetes, chronic obstructive pulmonary diseases and liver cirrhosis. Since most of these are also common risk factors for cancer among the general population, it may further suggest that the close link between AF and cancer could be partly explained by the sharing of common risk factors. For example, excessive amount of alcohol intake which could cause AF and liver cirrhosis was also important risk factor for cancers [28]. Furthermore, since smoking which could result in AF and chronic obstructive pulmonary disease was also carcinogenic [29], the link between COPD and cancer among AF patients could be partly mediated by smoking.

We also reported the incidences of cancers for patients having different numbers of risk factors. The risk of cancer continuously increased for patients with more risk factors. Therefore, prompt and detailed examinations are warranted for AF patients with multiple risk factors to early detect the occult malignancy. The previous study demonstrated that atherosclerotic cardiovascular diseases (ASCVDs), including coronary artery disease, aortic diseases and peripheral artery diseases, were associated with an increasing risk of cancers with a hazard ratio of 1.372 in the multivariate analysis [30]. Interestingly, ASCVDs were not independent predictors of cancers among AF patients in the present study. However, we were not able to exclude the possibility of underdiagnosis of ASCVDs in our claim database, and a further study is necessary to specifically investigate the association between ASCVDs and incident cancers among AF patients.

4.4. Study limitations

Our study is the largest population-based study to investigate the association between AF and cancer, and a major strength of our study is the use of a nationwide dataset, which enrolled a large sample of subjects. However, there are also limitations to consider. First, lifestyle factors, such as body mass index, exercise, cigarette smoking, detailed amount of alcohol consumption, and family history, which may know impacts on cancer occurrence, were not recorded in the NHI database. Second, information about the stages of incident cancers was not available. In our study, mortality occurred in 53.3% of patients after cancers being diagnosed and the mean durations to mortality were 1.23 years. These data may be helpful to partly understand the clinical severities of incident cancers. Lastly, the present study only enrolled Chinese patients, and whether the results can be extrapolated to other populations remains uncertain. However, we for the first time showed that the relationship between AF and cancer, which was primarily found among Caucasian populations, may also apply to Eastern Asians.

5. Conclusion

In the nationwide cohort study, we show that the risk of cancer was higher for AF patients compared to that of general population. The relative risk was higher early after an AF diagnosis but persisted in the long term. Age, male gender, hypertension, diabetes, chronic obstructive pulmonary diseases and liver cirrhosis are independent risk factors of cancer among AF patients. Prompt and detailed examinations may be considered for incident AF patients with multiple risk factors to early detect the occult malignancy. Further study is needed to assess the mechanisms underlying this association.

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Declaration of Competing Interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2019.08.021.

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