Antithrombotic therapy in the Netherlands: new insights from nationwide data

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CHAPTER

Epidemiology of coexisting atrial fibrillation and cancer in the Netherlands: prevalence, incidence, time trends, and associations with all-cause mortality

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Abstract

Background and Aims: Coexisting atrial fibrillation (AF) and cancer is not uncommon and challenges management of both conditions, for which epidemiological information is limited. The study aimed to provide comprehensive epidemiology of coexisting AF and cancer.

Methods: Using Dutch nationwide statistics, individuals with incident AF ("AF cohort") (n=320,139) and individuals with incident cancer ("cancer cohort") (n=472,745) were identified between 2015 and 2019. Dutch inhabitants without AF or cancer history, respectively, were matched to the cohorts by age, sex, immigration background, and income level as two corresponding control cohorts (n=320,135 and n=472,741). Prevalence of cancer/AF at baseline, incidence of developing cancer/AF (among those without cancer/AF at baseline) within one-year follow-up, and their time trends were determined. The association of developing cancer/AF during follow-up with all-cause mortality was estimated via time-dependent Cox regression analysis.

Results: The prevalence of cancer in the AF cohort was 12.6% (increasing from 11.9% in 2015 to 13.2% in 2019) compared with 5.6% in the matched controls without AF. The one-year risk of cancer was 2.5% (remaining stable over years) compared with 1.8% in the controls with an adjusted hazard ratio (aHR) of 1.52 (95%CI 1.46-1.58), which was similar by cancer type. The prevalence of AF in the cancer cohort was 7.5% (increasing from 6.9% to 8.2%) compared with 4.3% in the matched controls without cancer. The one-year risk of AF was 2.8% (remaining stable over years) compared with 1.2% in the controls with an aHR of 2.78 (95%CI 2.69-2.87), but several types of cancer (*i.e.*, cancer of oesophagus, lung, stomach, myeloma, and lymphoma) were associated with higher hazards of developing AF than other cancer types. Both developing cancer after incident AF (aHR 7.77, 95%CI 7.45-8.11) and developing AF after incident cancer (aHR 2.55, 95%CI 2.47-2.63) were associated with increased all-cause mortality, but the strength of the association varied by cancer type.

Conclusions: There is a bidirectional association between AF and cancer, and AF risk varies by cancer type. The burden of coexisting AF and cancer increased in recent years, and the development of one condition is negatively associated with survival of individuals with the other condition.

Introduction

Atrial fibrillation (AF) and cancer are both prevalent conditions in the general population, representing major health burdens [1,2]. AF is the most common arrhythmia and is related to unfavourable outcomes including stroke, heart failure, impaired quality of life, hospitalization, and death [3], while cancer has been the leading cause of death for years [4,5]. Both conditions were generally viewed as two distinct disease entities, but with cardio-oncology rapidly emerging as a new field, cardiovascular disorders including arrhythmias are increasingly recognised and considered in cancer patients [6-9]. The burden of the two conditions are both expected to increase with population aging and improvement in cancer survival [10-12], and the coexistence of one condition has been shown to make management of the other condition more challenging [13,14]. Studies have shown that cancer patients are facing increased risk of AF compared to those without cancer [15-18], and several underlying mechanisms have been proposed, such as shared risk factors/pathophysiology and side effects of cancer treatment [19,20]. However, there are still several knowledge gaps since currently available studies were generally derived from relatively outdated data and limited by a narrow cancer spectrum. It remains unknown how the burden of coexisting AF and cancer has changed in recent years, and whether AF affects cancer prognosis. In addition, the association between AF and cancer seems bidirectional [12,21], as new-onset AF has also been reported as a predictor of incident cancer [22,23], while this was so far under-recognized. As far as we know, no large-scale investigation has been performed into both directions within the same population. Given the immediate need for such relevant knowledge, we aimed to provide comprehensive epidemiology of coexisting AF and cancer bidirectionally, including prevalence, incidence, time trends, and associations with survival.

Methods

The study complied with the Declaration of Helsinki, and received an approval from the Scientific Committee of the Department of Clinical Epidemiology of the Leiden University Medical Center (No. A181) with a waiver of participant consent due to the use of pre-existing, de-identified data only. We followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline for cohort studies.

Data sources

The study used data accessed from Statistics Netherlands (in Dutch “Centraal Bureau voor de Statistiek”, CBS). CBS is a Dutch governmental institution that gathers and links de-identified individual data from various nationwide data sources. In the study we used nationwide data on household income, personal characteristics (*i.e.*, birthdate, sex, and immigration background), diagnoses registered within hospitalizations in Dutch hospitals

retrieved from discharge letters, death statistics, and outpatient medication prescriptions. Unless otherwise specified, diseases/conditions (including AF and cancer) were identified by diagnoses registered within hospitalizations. Details about the data sources and coding systems used for variable identification are provided in Supplementary Methods and Supplementary Table 1.

Study design and study populations

The study used a cohort study design, which included an incident AF cohort, an incident cancer cohort, and two corresponding matched control cohorts without AF or cancer, respectively, at baseline (Figure 1). Before identifying the specific cohorts, we first identified the Dutch inhabitants between 2015 and 2019 who were considered eligible for the study (*i.e.*, the source population). Eligible participants had to be registered in the nationwide data on household income and data on personal characteristics of the year upon entry in the study (i.e., one of the years between 2015 and 2019) and the prior five years.

From the source population, by examining data on diagnoses registered within hospitalizations, we identified individuals who had a diagnosis of AF or cancer for the first time between 1/1/2015 and 31/12/2019 as the incident AF cohort or the incident cancer cohort, respectively, after excluding those with diagnosis records of AF or cancer in the prior five years. For each individual in either cohort, the admission date of the hospitalization in which AF or cancer was diagnosed for the first time was referred to as the index date (*i.e.*, baseline) of the individual.

For each individual in the cohorts, we randomly sampled an individual from the source population as a control among those who met all of the following criteria: 1) alive on the index date; 2) with the same age (*i.e.*, absolute difference in birthdate ≤6 months), sex, immigration background, and level of standardised household income; 3) without a previous diagnosis record of AF (when matching for the incident AF cohort) or cancer (when matching for the incident cancer cohort) within five years before the index date (inclusive). A control would share the same index date of the individual from the incident AF/cancer cohort to whom he/she was matched. The sampling was with replacement. Details about the identification of source population and the cohorts are provided in Supplementary Methods and Supplementary Figure 1 to 2.

Determination of prevalent/incident cancer/AF

For the incident AF cohort and the corresponding matched control cohort (without AF history), we examined data on diagnoses registered within hospitalizations within five years before the index dates to determine whether an individual had prevalent cancer

(*i.e.*, cancer history) at baseline. If an individual happened to have a diagnosis record of cancer for the first time within the same hospitalization in which the index AF diagnosis was made, the cancer diagnosis would still be categorised as a prevalent diagnosis. For those without prevalent cancer at baseline, we further determined whether they would develop (incident) cancer by following them from the index date until the date of death, the admission date of the hospitalization in which cancer was diagnosed for the first time, or one year later, whichever came first. For the matched control cohort, subjects would also be censored when they developed AF during follow-up.

Similarly, in the incident cancer cohort and the corresponding matched control cohort (without cancer history), we determined whether an individual had prevalent AF (*i.e.*, AF history) at baseline or would develop (incident) AF within one year after the incident cancer diagnosis.

The investigated cancer types and other baseline characteristics

According to the diagnosis codes, we categorized all cancer into about 30 different types (Supplementary Table 2). In addition, we identified the following baseline characteristics: age, sex, immigration background, standardised household income, CHA_2DS_2-VASc score, HAS-BLED score, and various comorbidities (or medical history) including asthma, chronic obstructive pulmonary disease, other chronic lung diseases, heart failure, myocardial infarction, hypertension, rheumatic mitral stenosis/mechanical heart valves, other valvular heart diseases, peripheral artery diseases, liver diseases, gastroesophageal reflux disease, peptic ulcer disease, chronic kidney diseases, anaemia, coagulopathy, diabetes, thyroid diseases, ischemic stroke, transient ischemic attack, systemic arterial thromboembolism, Parkinson's disease, Alzheimer's disease, autoimmune diseases, systemic connective tissue disorders, venous thromboembolism, and major bleeding. Details about the identifications are provided in Supplementary Methods.

Statistical analysis

Baseline characteristics are presented as mean ± standard deviation, or numbers and percentages. Prevalence of cancer/AF at baseline in the incident AF/cancer cohort or the corresponding control cohort was calculated as the number of individuals with prevalent cancer/AF divided by the number of individuals in the cohort. Prevalence of cancer in the incident AF cohort (and the corresponding control cohort) was also presented per cancer type. Time trends in the prevalence were examined after stratifying the study cohorts by calendar years of the index dates.

After excluding those with prevalent cancer/AF at baseline, the incidence rates of developing cancer/AF in the incident AF/cancer cohort or the corresponding control

cohort were calculated as the number of individuals who developed cancer/AF during the follow-up divided by the total amount of observation time. In addition, cumulative incidences of developing cancer/AF and the corresponding cumulative incidence curves of a cohort were estimated by the cumulative incidence competing risk (CICR) method, in which all-cause death was considered as a competing event. For the matched control cohorts, subjects would also be censored when an individual developed the condition of the comparison cohort, which was also treated as a competing event. To compare incidence rates for AF or cancer between the cohorts, cause-specific Cox regression was used to estimate the hazard ratio (HR) and 95% confidence intervals (CIs). Three pre-specified adjustment models were employed: Model 1, adjusting for age, sex, immigration background, and standardised household income; Model 2, adjusting for Model 1 and CHA_2DS_2-VASc score, and HAS-BLED score; Model 3, adjusting for Model 1, and the above-mentioned various comorbidities (or medical history). The analyses were also repeated after stratifying the study cohorts by cancer types. Time trends in incidence of developing cancer/AF were examined after stratifying the study cohorts by calendar year of the index dates.

Developing cancer/AF during the one-year follow-up was further treated as a time-dependent exposure to estimate its association with all-cause mortality in the incident AF/cancer cohort (after excluding those with cancer/AF at baseline), and time-dependent Cox regression was employed to estimate the HRs and 95%CIs with the above-mentioned adjustment models. The control cohorts were not involved in this analysis.

All statistical analyses were performed with SPSS® Statistics (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.) and R program (R Core Team (2018). R Foundation for Statistical Computing, Vienna, Austria. Available online at https://www.R-project.org/).

Results

Baseline characteristics of the study cohorts

A total of 320,139 individuals were included as the incident AF cohort, to whom 320,135 subjects were matched as the control cohort without AF history, with a mean age of 74.6±11.9 years and a male proportion of 55.8%. Compared to the control cohort, the incident AF cohort had higher CHA_2DS_2-VASc score and HAS-BLED score, and higher prevalence of all the investigated comorbidities [hypertension (39.1%), heart failure (21.1%), and diabetes (19.4%)]. Regarding types of incident AF, most (74.6%) were unspecified AF. Details are provided in Supplementary Table 3.

Prevalence of cancer in the AF cohort and prevalence of AF in the cancer cohort

As presented in Figure 2 and Supplementary Table 3, 12.6% of individuals in the AF cohort had prevalent cancer at baseline, among which cancer of ill-defined or multiple sites (4.3%), prostate (2.7%, among the male), breast (2.3%, among the female), colon/rectum (2.1%), and lung (2.0%) were the most prevalent types. The control cohort without AF history had a similar distribution of prevalent cancer types, but the prevalence (overall 5.6%) was generally lower than that in the AF cohort, particularly for cancer of the lung (0.3% versus 2.0%), leukaemia (0.1% versus 0.6%), oesophagus (0.1% versus 0.5%), lymphoma (0.2% versus 0.8%), and myeloma (0.1% versus 0.4%). In the incident cancer cohort, 7.5% had AF history at baseline, while in the matched control cohort without a cancer history, this was only 4.3%.

Incidence of developing cancer in the AF cohort and developing AF in the cancer cohort

After excluding individuals (n=40,224) with prevalent cancer from the AF cohort, 2.54% (95%CI 2.48-2.60%) developed cancer within one year, while this was 1.80% (1.75-1.84%) in the control cohort without AF history, leading to an adjusted HR (aHR, by Model 3) of 1.52 (95%CI 1.46-1.58). Cancer occurred more frequently in the first three months after the incident AF diagnosis than in the months later (Figure 3), and such a time course was consistently observed for most cancer types (Supplementary Figure 3 to 32). The most frequently developed cancer types were the same between the two cohorts (with similar relative risk estimates, Figure 4), namely cancer of ill-defined or multiple sites, prostate (among the male), breast (among the female), colon/rectum, and lung.

After excluding individuals (n=35,483) with prevalent AF from the cancer cohort, 2.84% (95%CI 2.79-2.89%) developed AF within one year, which proportion was 1.19% (95%CI 1.16-1.22%) in the control cohort without cancer history, with an aHR of 2.78 (95%CI 2.69-2.87). AF also occurred more frequently in the early stage after the incident cancer diagnosis than in later stages, particularly in the first three months (Figure 3). When stratifying by cancer types, such a time course of developing AF was also consistently observed for most cancer types (Supplementary Figure 3 to 35), but for individuals with cancer of the oesophagus, AF appeared to develop most frequently in the 3rd-6th month after the incident cancer diagnosis (Supplementary Figure 4). Although individuals with any of the investigated cancer types generally had higher risk of developing AF than the control cohort (Figure 5), several cancer types, including cancer of oesophagus (aHR 9.63, 95%CI 8.89-10.43), lung (aHR 6.27, 95%CI 5.92-6.64), stomach (aHR 5.73, 95%CI 5.07-6.47), myeloma (aHR 5.18, 95%CI 4.65-5.77), and lymphoma (aHR 4.24, 95%CI 3.91-4.59), yielded higher relative risk estimates for developing AF than the other

cancer types. Details about baseline characteristics of the study cohorts after excluding those with prevalent cancer/AF, and about the results of incidence analysis are provided in Supplementary Table 4 to 6.

Time trends in coexisting AF and cancer

When the study cohorts were stratified by calendar years of the index dates, we found that the prevalence of cancer upon incident AF diagnosis increased from 11.9% in 2015 to 13.2% in 2019, while such a trend was also observed in the matched control cohort without AF history (*i.e.*, from 5.4% to 5.7%). Similarly, an increasing prevalence of AF upon incident cancer diagnosis was found as well as in the control cohort without cancer history (*i.e.*, from 6.9% to 8.2%, and from 3.9% to 4.6%, respectively). The incidence of developing cancer or AF, however, remained constant between years (Figure 6). Details about baseline characteristics of the study cohorts in different calendar years and about the results of time trend analyses are provided in Supplementary Table 7 to 16.

Association between developing cancer or AF and all-cause mortality

As presented in Figure 7 and Supplementary Table 17, in individuals in the incident AF cohort who had no cancer history at baseline, developing cancer within one year (as a time-dependent exposure) was associated with increased all-cause mortality (aHR 7.77, 95%CI 7.45-8.11). The association was strongest for cancer of the brain (aHR 25.99), other lymphoid/hematopoietic tissue (aHR 16.18), mesothelial/soft tissue (aHR 7.49), ill-defined or multiple sites (aHR 7.10), and lymphoma (aHR 7.08). For individuals in the cancer cohort without AF history at baseline (Figure 7 and Supplementary Table 18), developing AF within one year was also associated with increased all-cause mortality (aHR 2.55, 95%CI 2.47-2.63%), and the strongest associations were observed in those with cancer of endocrine glands (aHR 10.12), other skin cancer (aHR 7.74), melanoma (aHR 5.55), bone/cartilage (aHR 5.30), and other respiratory/ intrathoracic organs (aHR 4.90).

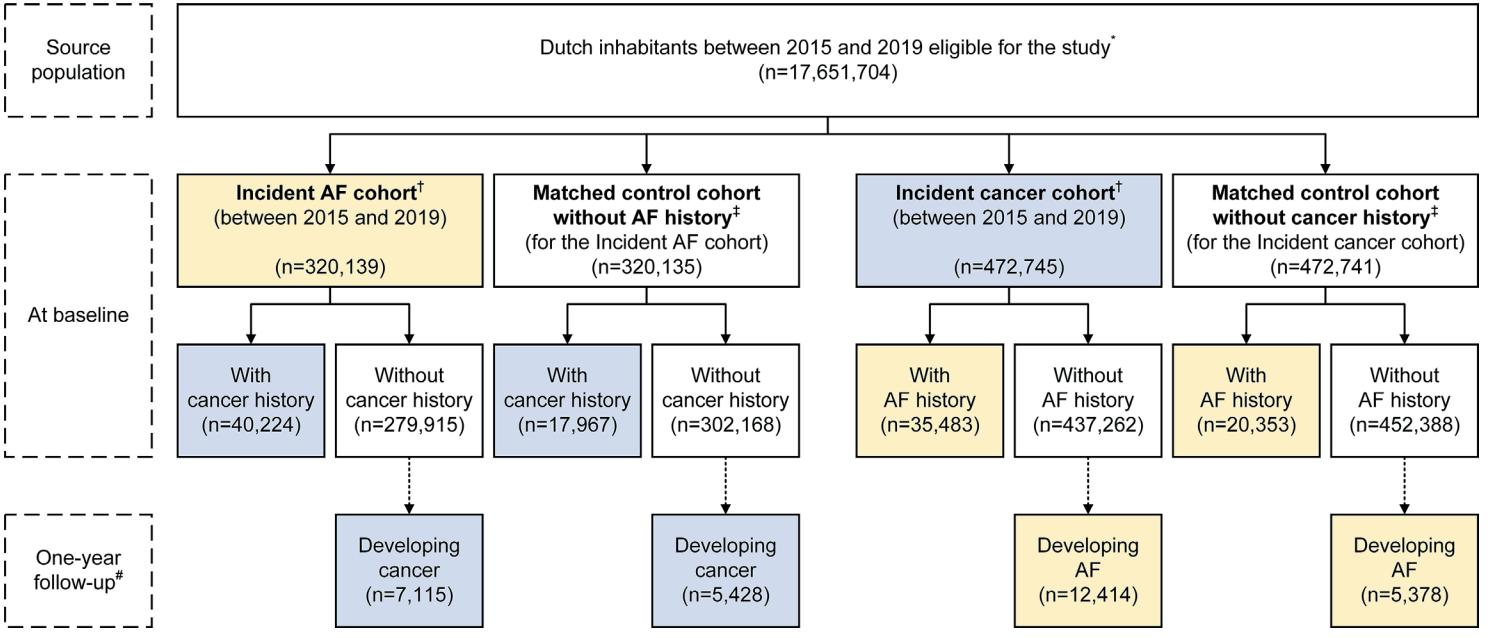


Figure 1: Illustration of the study design and inclusion of the study populations.

* Details about the identification of Dutch inhabitants between 2015 and 2019 who were considered eligible for the study are provided in Supplementary Figure 1.

† A diagnosis of AF (or cancer) was considered incident when there was no previous diagnosis record of AF (or cancer) within the prior five years (see Supplementary Figure 2).

‡ There were 305,999 unique individuals among the matched control cohort without AF history (for the incident AF cohort), and 454,940 unique individuals among the matched control cohort without cancer history (for the incident cancer cohort).

The follow-up started from the index date of each individual until one year after, or when the outcome event first occurred (i.e., developing cancer or AF), or date of death, whichever came first. For the matched control cohort, they would also be censored if they developed AF (or cancer).

Abbreviation: AF, atrial fibrillation.

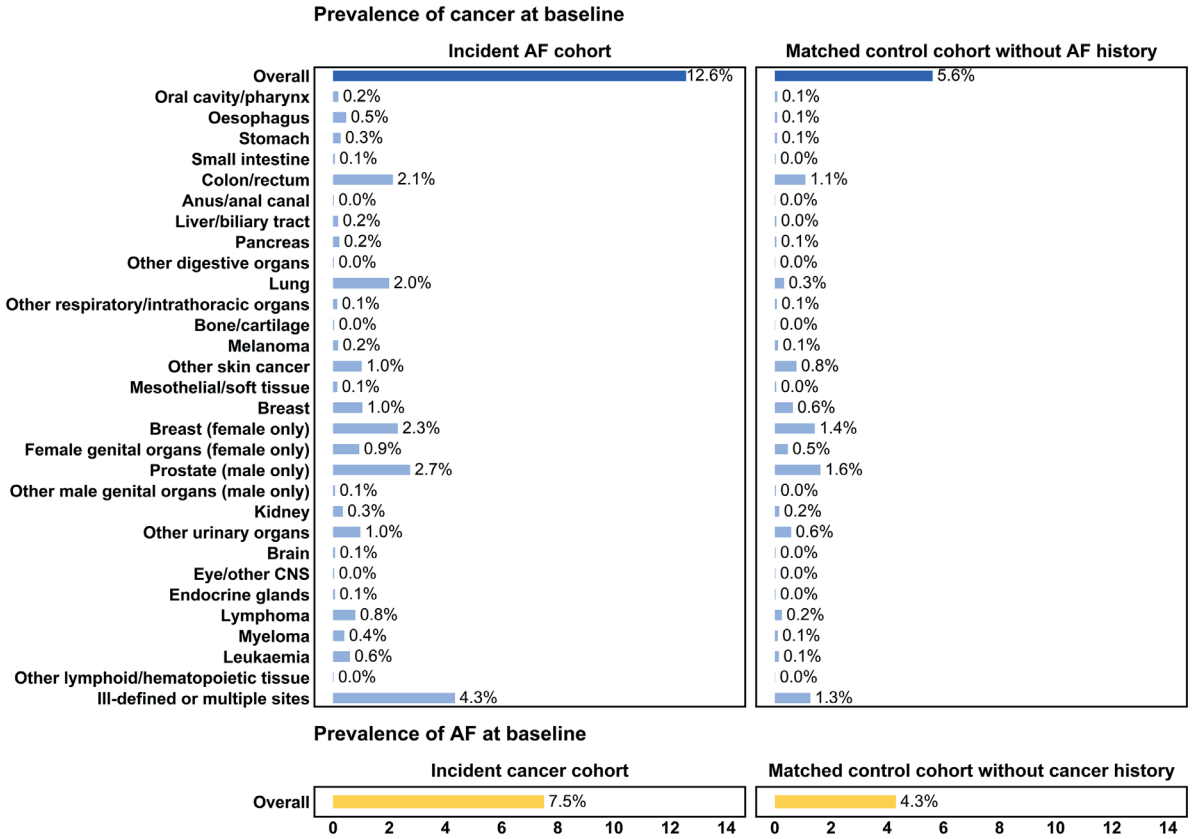


Figure 2: Prevalence of cancer among the incident AF cohort and prevalence of cancer among the incident cancer cohort versus that in the control cohorts.

For readability, the names of cancer types in the figure were shortened. Detailed descriptions can be found in Supplementary Table 2.
Abbreviation: AF, atrial fibrillation; CNS, central nervous system.

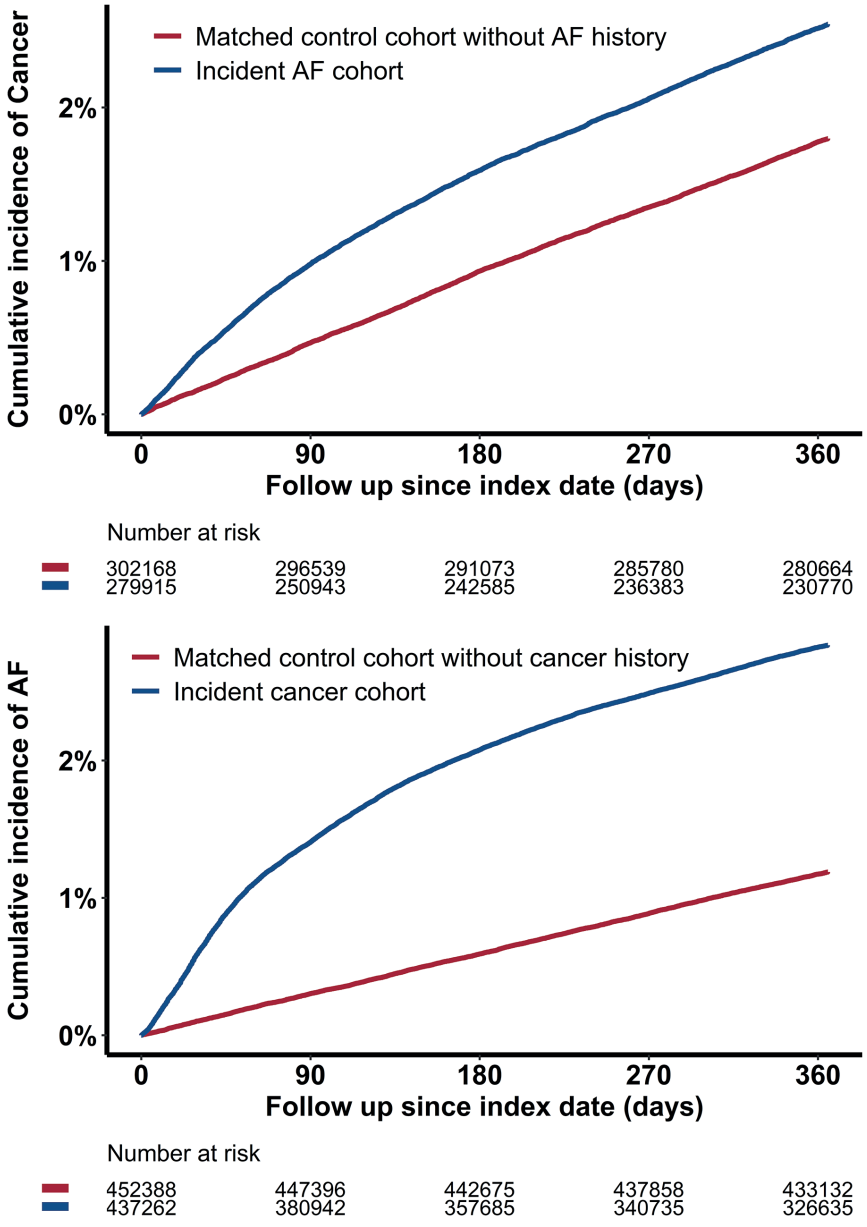
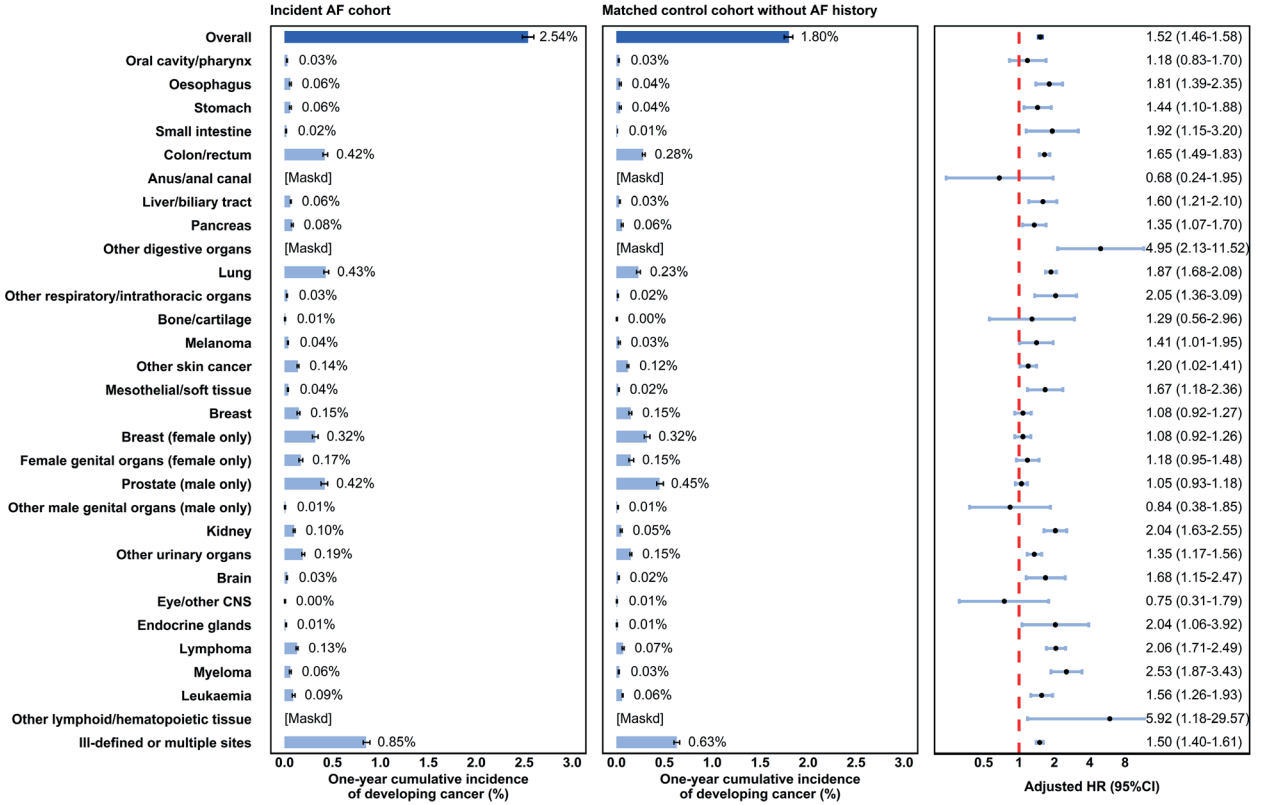


Figure 3: Cumulative incidence curves for developing cancer after incident AF or developing AF after incident cancer versus that in the control cohorts.
Individuals who had history of cancer (or AF) at baseline were excluded from this analysis. The cumulative incidence curves were plotted using the cumulative incidence competing risk (CICR) method, in which all-cause death was considered as a competing event. The control cohorts would also be censored when developing AF (or cancer) during the one-year follow-up, which was also considered as a competing event.
Abbreviation: AF, atrial fibrillation.



The HRs refer to the hazard of developing cancer (overall, or of a specific type) in the incident AF cohort compared to that in the control cohort, which were estimated by cause-specific Cox regression, after adjusting for age, sex, immigration background, standardised household income, and various comorbidities (or medical history).

Abbreviation: AF, atrial fibrillation; CNS, central nervous system; HR, hazard ratio; CI, confidence interval.

Figure 4: One-year cumulative incidence of developing cancer after incident AF versus that in the control cohort.
For readability, the names of cancer types in the figure were shortened. Detailed descriptions can be found in Supplementary Table 2. Individuals who had history of cancer at baseline were excluded from this analysis. The cumulative incidence was estimated by the cumulative incidence competing risk (CICR) method, in which all-cause death was considered as a competing event. The control cohort would also be censored when developing AF during the one-year follow-up, which was also considered as a competing event.

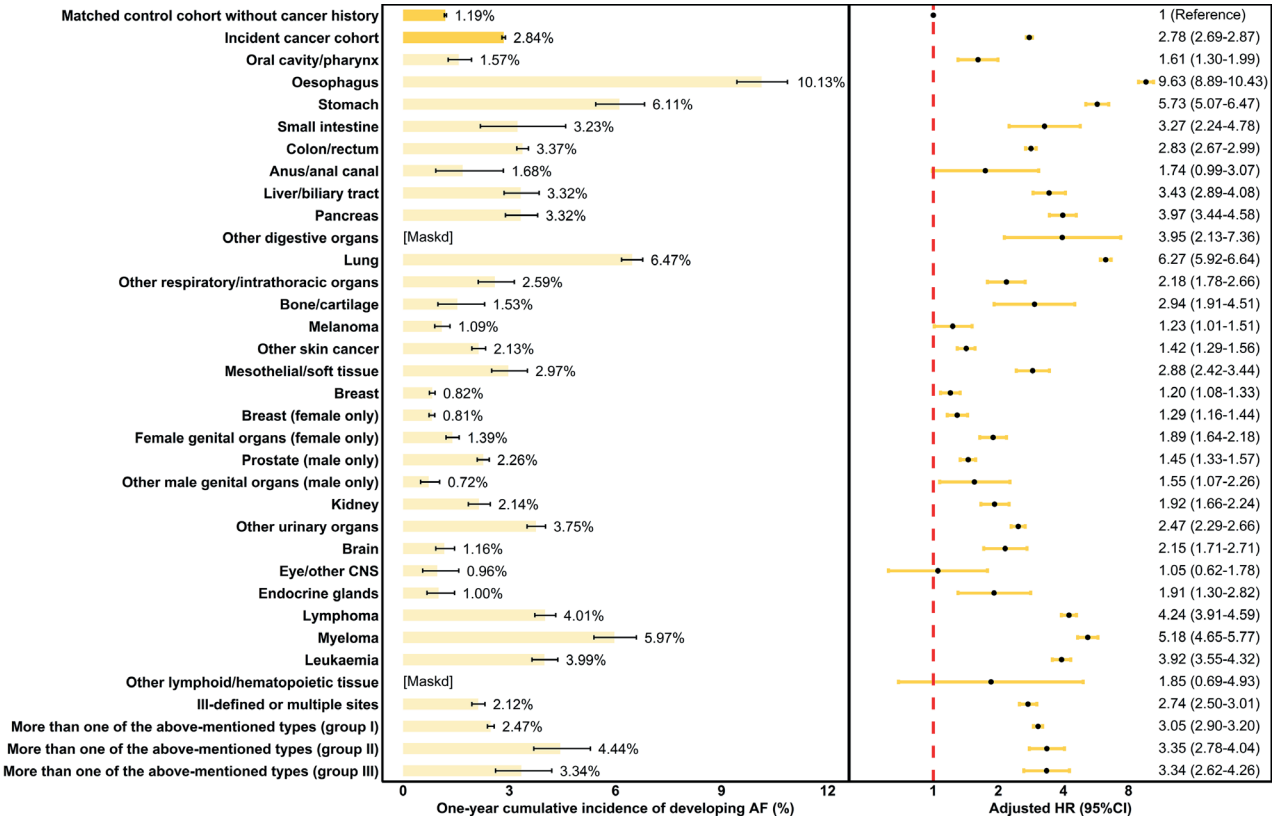


Figure 5: One-year cumulative incidence of developing AF after incident cancer versus that in the control cohort.
For readability, the names of cancer types in the figure were shortened. Detailed descriptions can be found in Supplementary Table 2. Individuals who had history of AF at baseline were excluded from this analysis. The cumulative incidence was estimated by the cumulative incidence competing risk (CICR) method, in which all-cause death was considered as a competing event. The control cohort would also be censored when developing cancer during the one-year follow-up, which was also considered as a competing event.

The HRs refer to the hazard of developing AF in the incident cancer cohort (overall, or of a specific type) compared to that in the control cohort, which were estimated by cause-specific Cox regression, after adjusting for age, sex, immigration background, standardised household income, and various comorbidities (or medical history). For female or male specific cancer (as indicated), only the female or male individuals in the control cohort were included as reference group.

Abbreviation: AF, atrial fibrillation; CNS, central nervous system; HR, hazard ratio; CI, confidence interval.

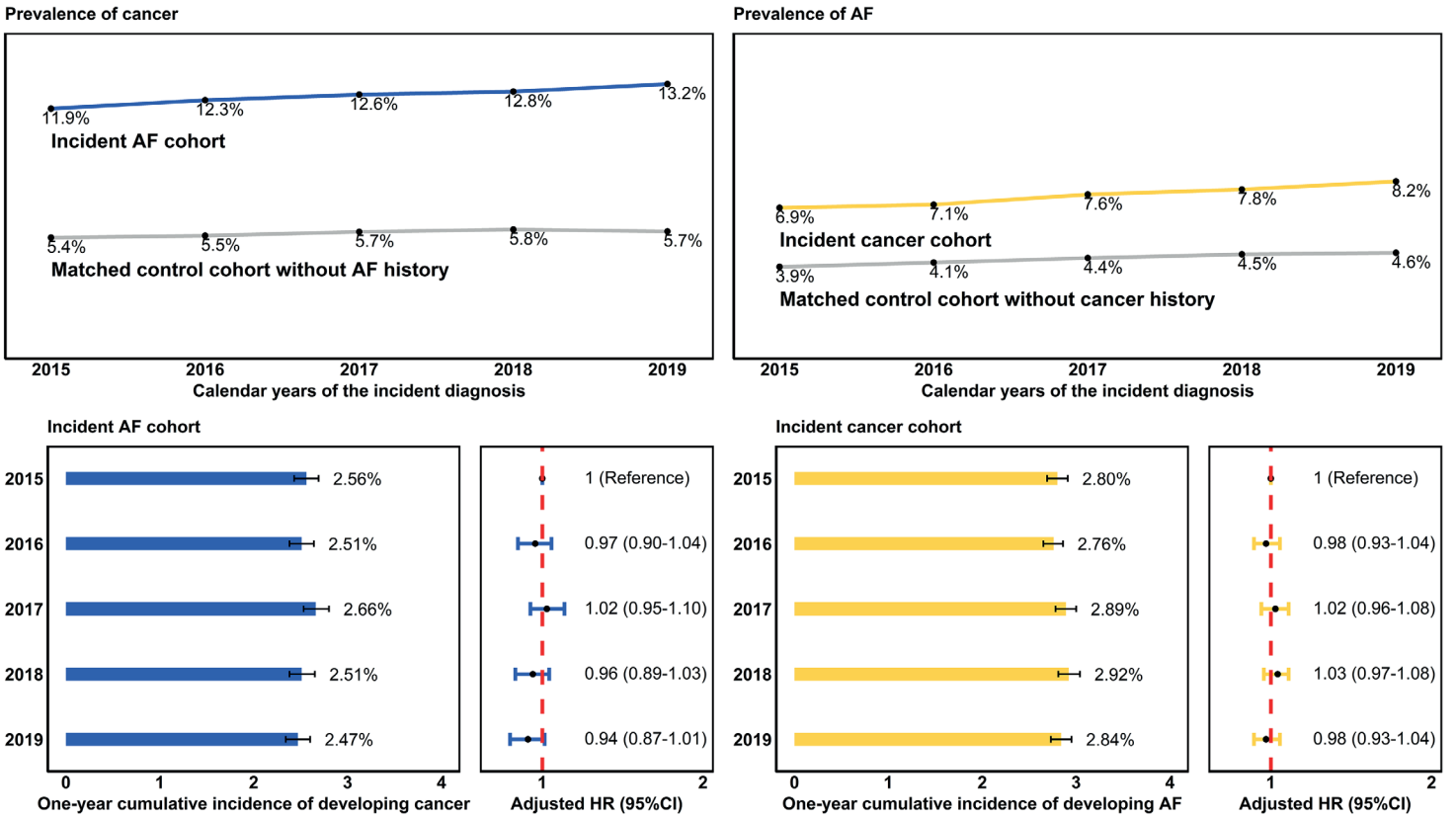
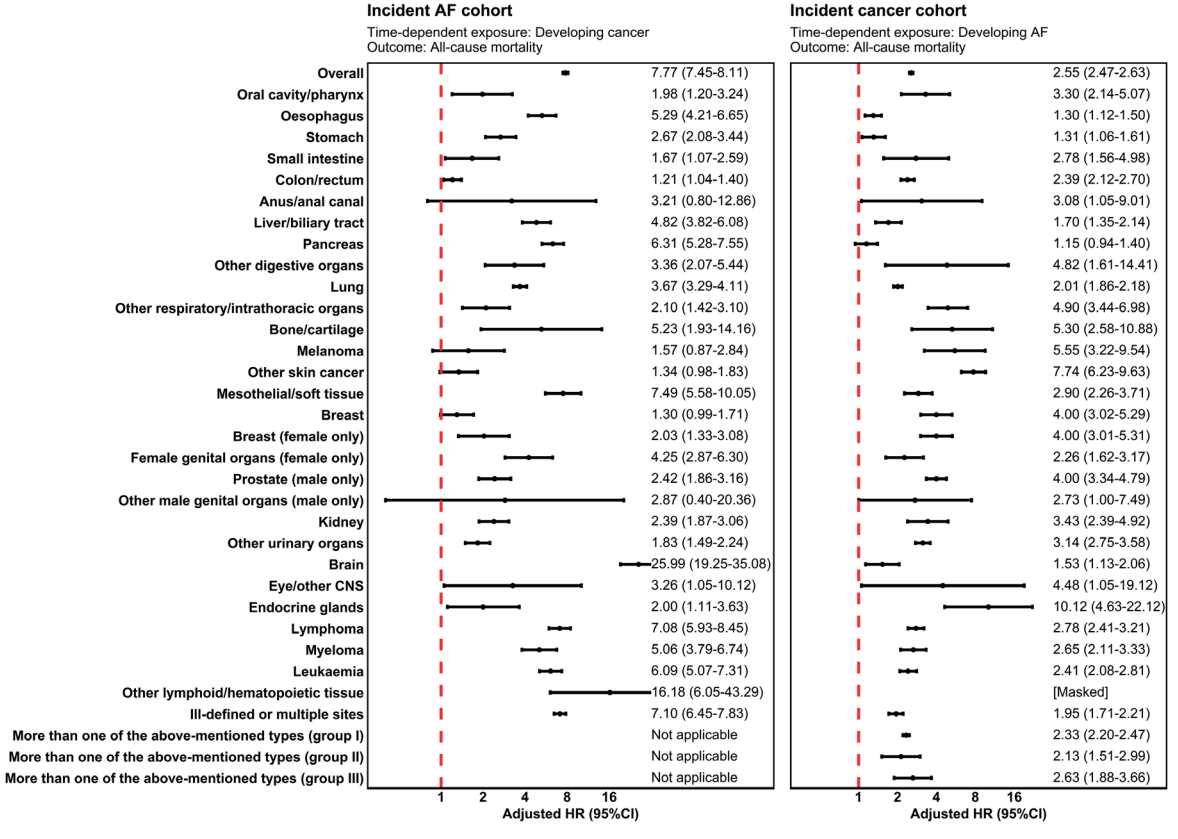


Figure 6: Time trends in coexisting AF and cancer.
The HRs refer to the hazard of developing cancer/AF in the incident AF/cancer cohort diagnosed in different calendar years compared to that of the same cohort diagnosed in 2015, which were estimated by cause-specific Cox regression, after adjusting for age, sex, immigration background, standardised household income, and various comorbidities (or medical history). Abbreviation: AF, atrial fibrillation; HR, hazard ratio; CI, confidence interval.



Individuals who had history of cancer (or AF) at baseline were excluded from this analysis. The individuals were followed for one year after incident AF (or cancer) diagnosis, or until all-cause mortality, whichever came first, while developing cancer (or AF) during the follow-up was treated as time-dependent exposure to estimate its association with all-cause mortality estimated by multivariable Cox regression, with adjustment for time-fixed covariates (identified at baseline), including age, sex, immigration background, standardised household income, and various comorbidities (or medical history). For the analyses of developing non-sex specific cancer among the incident AF cohort, the individuals were also censored when developing sex specific cancer, and vice versa (as indicated).

Figure 7: Association of developing cancer/AF after incident AF/cancer with all-cause mortality.
For readability, the names of cancer types in the figure were shortened. Detailed descriptions can be found in Supplementary Table 2.
Abbreviation: AF, atrial fibrillation; CNS, central nervous system; HR, hazard ratio; CI, confidence interval.

Discussion

In the current study, we thoroughly examined the epidemiology of coexisting AF and cancer. Our main findings included: (1) AF and cancer are commonly coexisting, and the prevalence of having one condition among those with the other was increasing in recent years; (2) compared to the general population, having one condition is associated with an increased risk of developing the other, and both risks are the highest during the first three months; (3) the types of cancer that are more likely to develop after AF are in line with the most frequent cancer types in the general population, while individuals with some types of cancer are noticeably more likely to develop AF than those with other cancer types; (4) newly developing cancer is associated with increased all-cause mortality among AF patients, and vice versa, but the strength of the association with mortality varies by cancer type.

Implications of the findings

Since our investigation was based on a recent (2015-2019) and unselected nationwide population, which covered both directions (*i.e.*, occurrence of cancer after AF, and occurrence of AF after cancer) and various cancer types, the findings present recent and comprehensive epidemiological knowledge about coexisting AF and cancer, including prevalence, incidence, time trends, and associations with survival. These detailed statistics about both absolute and relative risk as well as the time course cover the complete cancer spectrum, pointing out what cancer types should receive more attention in clinical management and research regarding the issue of comorbid AF and vice versa. Results of the time trend analysis indicate an increasing burden of coexisting AF and cancer, which has not been reported before and might warrant awareness. The investigations into multiple cancer types, together with the inclusion of the matched control cohorts from general population, reveal that the distribution of cancer types that occur in AF patients is similar to the general population, whereas in the opposite direction, AF occurred more frequently after some cancer types than others, which deepens the understanding of the bidirectional associations between AF and cancer. Last but not least, the associations we observed between coexisting AF and cancer and survival raise the question whether preventing and better managing one condition would benefit the prognosis of those with the other condition. In short, the abundant epidemiological information from our study will help fulfil the immediate need of the rapidly emerging field of cardio-oncology, and at the same time feeds new and relevant research questions.

AF after cancer

The growing recognition of the link between cardiovascular diseases and cancer may stem from the combination of the aging population, improved cancer management that

prolongs survival, and the introduction of novel cancer therapies that bring cardiovascular toxicity [7,21,24,25]. As a result, existing epidemiological investigations mainly focused on occurrence of AF in cancer patients, either for a specific cancer type or treatment [26-34] or multiple cancer types [15-18]. A meta-analysis found cancer patients had a 47% higher risk of developing AF compared to those without cancer, especially in the first three months [35]. What we observed is overall consistent with these findings, but what we added to this topic is that we included a much more recent study population (2015-2019) and investigated more granular cancer types. This makes our findings better reflect recent practice, which is relevant given the rapid advances in cancer management. In addition, our study cohorts were defined under strict and the same criteria, in which each individual by design had a complete one-year follow-up (unless death), and many covariates were included for comparisons with the general population. However, it should be noted that the increased risk of AF in cancer patients cannot be simply interpreted as a causal relationship, since residual confounding could not be ruled out in the observational study design we used.

We found there was an increasing trend in prevalence of AF among cancer patients over the years, but the incidence of developing new AF remained stable. Since we also observed an increasing trend in AF prevalence in the general population, aging might partly explain the increase in AF prevalence in the cancer patients. It is worth mentioning that due to data limitation, we could not distinguish which condition actually occurred first when both AF and cancer were diagnosed for the first time within the same hospitalization. When this was the case, we would always classify the AF as a prevalent AF, and therefore we might have underestimated the incidence of AF, particularly for AF that actually occurred immediately after the incident cancer diagnosis. However, since these cases only accounted for 2.2% of the incident cancer cohort, this should have had limited impact, and moreover, it would only suggest that the true comorbidity burden of coexisting AF and cancer is actually more substantial than we observed.

With respect to the incidence of AF by cancer type, we found that individuals with cancer of oesophagus, lung, stomach, myeloma, and lymphoma faced the highest risk of AF. This finding was also generally consistent with other studies, although the size of the risk might differ. For example, in the study by Yun et al [15], myeloma and oesophageal cancer were found to be strongly associated with AF, but stomach cancer showed the lowest association with AF among the investigated solid cancers. This could be due to the difference in cancer epidemiology (*e.g.*, regarding cancer grade/stage/treatment upon initial diagnosis) between regions/countries, which we could not further examine due to lack of such data. The findings from a Danish study [16] somewhat supported the above speculation, as the incidence of AF after lung cancer was the highest (among the cancer

types they investigated), followed by upper gastrointestinal cancer, which is consistent with what we found.

Regarding time course, although AF tended to develop more frequently in the first three months after a cancer diagnosis, there were variations between cancer types, which might be explained by difference in anticancer treatment trajectory. For example, among patients with cancer of oesophagus we found that AF frequently developed in the first six months, particularly during the 3rd-6th month. In future studies, it would be interesting to explore what causes such a pattern (*e.g.*, surgical treatment performed after preoperative chemoradiotherapy [36]).

Another naturally raised question is what might explain the association between cancer and AF. Our study cannot provide an answer directly, but several potential explanations have been proposed previously [19,20], including common risk factors/pathophysiology, cancer treatment that may induce AF (*e.g.*, radiation therapy, chemotherapy, major transthoracic surgery, and targeted therapy), paraneoplastic effects, and detection bias (*i.e.*, more electrocardiogram (ECG) examinations are performed after a cancer diagnosis, leading to more AF diagnoses). It is very likely that multiple mechanisms contribute to the increased AF risk in cancer patients, either directly or indirectly, causally or non-causally.

Previous studies have shown that AF was associated with adverse outcome events in various types of cancer [26,37-42], but as far as we know, no study investigated this association across multiple cancer types in the same source population. We found that in cancer patients, developing AF was associated with increased all-cause mortality after adjusting for the various baseline characteristics, but the association seemed to vary by cancer type. This again raises more research questions to explore in the future, but it should also be realised that our findings cannot be interpreted in a causal way, as AF itself might be caused by advanced cancer therapeutics used for advanced cancer [43,44].

Cancer after AF

In the opposite direction of the association, evidence about the occurrence of cancer after AF is very limited [22]. According to a recent meta-analysis [23], which included five cohort studies [45-49] and a case-control study [50], new-onset AF was associated with a 24% increase in cancer risk during the initial 90 days but not after, and the association was found only for lung cancer but not colorectal cancer and breast cancer. Besides these studies, there were only three other studies that investigated the association of developing cancer after AF: Müller et al [51] found that AF tended to be one of the diseases diagnosed preceding colon cancer; Ostenfeld et al [52] reported that 2.5% of incident AF patients were diagnosed with cancer within three months; Kahr et al [53] found that participants undergoing screening

colonoscopy who had AF showed a higher burden of colorectal cancer. Compared to these findings, we found that incident AF was associated with an overall 52% increase in cancer risk and that cancer was diagnosed most frequently in the first three months after AF diagnosis. The strengths our study had when investigating AF developed after cancer also applied to this investigation, including the well-defined study cohorts, the investigation into time trends, the coverage of different cancer types, and the adjustment for various baseline characteristics.

Since we found the types of cancer that are more likely to develop after AF were generally in line with that in the general population, our findings do not seem to support AF as a cause of new-onset cancer (instead, *e.g.*, detection bias), although again, our data and study design was unable to examine a causal relationship. There are several potential mechanisms, including radiation exposure during AF ablation (which was, however, not supported by a further investigation [54]), anticoagulant-related bleeding leading to early diagnosis of cancer [55-58], incidental imaging findings for AF ablation [59,60], and potential cancer risk carried by some medications used for AF [61]. A recent Mendelian randomization study did not support a causal role of AF in increasing cancer risk [62]. These speculations should be interpreted with caution, and remain to be confirmed.

Nevertheless, the increasing time trend over the years we observed in prevalence of cancer among incident AF patients is relevant to know, since AF patients require long-term management [3], while comorbid cancer has been shown to challenge AF management (particularly about anticoagulation) [63-66]. This AF subpopulation (*i.e.*, with cancer) has attracted increasing attention [8], but there are still many knowledge gaps. For example, the CHA_2DS_2-VASc and HAS-BLED score seem to show suboptimal performance in AF patients with cancer [67,68], which challenges treating these patients optimally. Taking this relevance into account, even if AF is non-causally associated with cancer, it might be worthwhile to examine whether there is a role for cancer screening among individuals with newly diagnosed AF, although cost-effectiveness and potential harms should be also considered.

Limitations

There are several other limitations in our study. First, we only used routinely collected data, which is likely to have introduced some misclassification. This limitation especially applies to our identification of AF and cancer, for which only data on diagnoses made within hospitalization were used. As individuals with AF or some type of "mild" cancer might not necessarily be admitted to hospital, we might have under-recognized them. The same identification strategy in our previous studies suggests this might not be a

major concern [69,70], and still, the prevalence and incidence we observed were still rather substantial, despite this possible underestimation. The date of an incident diagnosis of AF/cancer we used was the admission date of the hospitalization in which the diagnosis of AF/cancer was first made. Therefore, our findings about the time course of developing cancer/AF might differ from studies that identified the index dates in a different way (*e.g.*, via outpatient diagnosis). Ideally, screening for AF with better approaches (such as ECG, wearable photoplethysmography-enabled device) [71] is needed to precisely evaluate the burden of AF among cancer patients, which should be considered in further investigations. Second, no data on cancer stage/grade were available. Third, we limited the follow-up to one year only, and we could not distinguish whether a previous cancer diagnosis was cured or active when analysing the incident AF cohort. In addition, we only investigated the association of developing cancer/AF with all-cause mortality, without examining other relevant outcome events (*e.g.*, progression-free survival, ischemic stroke, etc). These remain relevant research directions for the future.

In conclusion, there is an important bidirectional association between AF and cancer, and AF risk varies by cancer type. The burden of coexisting AF and cancer increased in recent years, and the development of one condition is negatively associated with survival of patients with the other condition. Awareness of this comorbidity burden should be raised in both AF and cancer patient populations, and further explorations of the underlying mechanisms and of optimal management are warranted.

The supplements are accessible through scanning the QR code.

In case of an invalid QR code, email: qingui4ch@gmail.com

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