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New-onset atrial fibrillation as a predictor of cancer: Insights from a real-world dataset

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ABSTRACT

BACKGROUND A bidirectional relationship between atrial fibrillation (AF) and cancer has been suggested, but the mechanisms and directionality remain poorly understood.

OBJECTIVE This study aimed to examine the relationship between new-onset AF and incident cancer across different age groups.

METHODS This retrospective study used the TriNetX research network. Patients with hypertension, type 2 diabetes, or coronary artery disease were included and stratified by the presence of AF. Individuals with previous malignancy were excluded. Patients were categorized into 3 age groups (30–50, 50–70, and 70–85 years) and matched 1:1 using propensity scores. The primary outcome was all-cause cancer incidence, with secondary analyses of site-specific malignancies. Risk ratios, Kaplan–Meier survival analysis, and multivariable Cox regression models were used. Follow-up was up to 15 years after AF diagnosis.

RESULTS Matched cohort sizes were 30–50 ($n = 67,156$ per group), 50–70 ($n = 510,308$), and 70–85 years ($n = 882,729$). AF was associated with an increased cancer risk: relative risks of 2.99, 1.79, and 1.49 across increasing age groups (all $P < .001$). Kaplan–Meier analyses showed decreased cancer-free survival: hazard ratios of 2.96, 1.84, and 1.53 across increasing age groups (all $P < .001$). Sensitivity analyses excluding cancers diagnosed within the first 3 months and after the first year of AF onset, comparing AF subtypes, and using multivariable Cox models confirmed consistent associations.

CONCLUSION AF is associated with an increased risk of incident cancer, particularly in younger individuals.

KEYWORDS Atrial fibrillation; Atrial arrhythmia; Cancer; Cardio-oncology; Epidemiology

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Atrial fibrillation (AF) is the most frequent cardiac arrhythmia encountered in clinical practice. Its prevalence in the general population is estimated at 2%, increasing to 10%–12% in patients older than 80 years.¹ Our understanding of the pathophysiological mechanisms that underlie AF has progressed significantly, which includes a combination of atrial fibrosis, oxidative stress, inflammation, lifestyle factors, diet, and genetic factors.²

The prevalence of cancer has steadily increased as the mortality rates for several cancers have declined in the setting of advanced therapies, allowing patients to live longer with cancer.³ With the incidence of AF increasing with age, the

proportion of patients living with both AF and cancer can only be expected to increase.

The relationship between AF and cancer has been increasingly recognized, with studies suggesting a bidirectional association.⁴ On one hand, cancer may predispose individuals to AF through mechanisms such as systemic inflammation, stress, autonomic dysfunction, electrolyte abnormalities, infection, or direct myocardial effects of tumor infiltration or cytotoxic therapy.^{5–7} On the other hand, AF and cancer may arise independently owing to shared risk factors, including aging, obesity, smoking, alcohol use, and chronic comorbidities, raising the possibility of co-

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occurrence without direct causality.^{8,9} Recent observational studies have reported an elevated incidence of cancer diagnoses shortly after the onset of AF, particularly within the first 3 months, suggesting that AF may serve as a clinical marker of occult malignancy rather than a direct cause.^{10,11}

Given the significant morbidity and mortality associated with both AF and cancer, further investigation into their temporal relationship may have important implications for clinical surveillance and risk stratification. We aimed to explore the relationship between patients with newly diagnosed AF and incident cancer diagnosis using the TriNetX research network.

Methods

Study design

We performed a retrospective observational study comparing the impact of AF with no AF on incident cancer diagnoses. A flowchart of the study design is presented in the [Supplemental Index \(Supplemental Figure 1\)](#).

Data source

This study used data from the TriNetX research network (TriNetX, Inc). TriNetX is a global federated health research network providing access to electronic medical records (diagnoses, procedures, medications, laboratory values, genomic information) across large health care organizations (HCOs). As a federated network, TriNetX received a waiver from the Western Institutional Review Board given that only aggregated counts and statistical summaries of deidentified information were received. This query was run on the "Research" network that contains data on more than 115 million patients across 105 HCOs, predominantly in the United States. All HCOs in the network were queried, and 90 responded.

Patient selection

Patients were identified based on the International Classification of Diseases, Tenth Revision, diagnosis and procedure codes ([Supplemental Index, Supplemental Table 1](#)). We included patients with a history of hypertension, coronary artery disease, or type 2 diabetes. Patients were then stratified by the presence of AF. All AF types were included. Patients with a history of malignancy were excluded.

Age groups

The study groups were subdivided by age into the following groups: 30–50, 50–70, and 70–85 years. This was done to assess the impact of AF on cancer across age groups and limit the group sizes for adequate propensity score matching.

Index event and follow-up

The index event defines the point in time when each patient in the cohort enters the analysis. In the AF group, the

index event was defined as the date when both AF and at least 1 of the previously mentioned comorbidities were first concurrently fulfilled. In the no-AF group, the index event was defined as the date of first diagnosis of any of the 3 comorbidities. Follow-up for both cohorts extended up to 15 years from the index date.

Propensity score matching and covariates

Propensity score matching was conducted using TriNetX's built-in functions to generate 1:1 matched cohorts based on key confounders: demographics (age, race, gender), comorbidities (obesity, smoking, alcohol use, hormone replacement therapy), medications (antilipemics, aspirin), and laboratory values (hemoglobin A1c). Propensity score density is presented in [Supplemental Figures 2–4](#).

Outcomes

The primary outcome was a composite of all cancer types, excluding skin cancer and melanoma. Secondary outcomes were individual cancer types.

Statistical analysis

All statistical analyses were performed using built-in functions of the TriNetX platform. Baseline characteristics were expressed as a mean and standard deviation for continuous variables and as a number and percentage for categorical variables. The baseline characteristics were compared with the χ^2 test for categorical variables and the Student t test for continuous variables. Propensity score matching was conducted to create a 1:1 ratio between cohorts using a nearest-neighbor greedy matching algorithm with a caliper width of 0.1 pooled standard deviations. Any variable exhibiting a standardized difference of <0.1 between the 2 groups indicated adequate matching. Risk ratio analyses were performed to compare the proportion of patients experiencing the outcomes of interest and calculate relative risks (RRs). These estimates reflect cumulative incidence and are not derived from logistic regression. Kaplan–Meier analyses, coupled with log-rank tests, were used to estimate and compare the incidence of outcomes over time and calculate hazard ratios (HRs). Multivariable Cox proportional hazards regression models were constructed to assess the independent association between AF and incident cancer while adjusting for relevant covariates. A *P* value threshold of <.05 was used to determine statistical significance.

Results

Baseline characteristics

All baseline characteristic data are presented in [Table 1](#). In the 30–50 age group, our query resulted in 67,748 patients with AF and 3,015,114 patients without AF. After propensity matching, there were 67,156 patients in both groups. The mean age in both groups was 38.8 ± 6.4 .

In the 50–70 age group, our query resulted in 537,022 patients with AF and 7,431,825 patients without AF. After

Abbreviations

AF: atrial fibrillation

Table 1 Baseline characteristics—initial cohort

Variable	Age 30–50 y			Age 50–70 y			Age 70–85 y		
	Before propensity matching		After propensity matching	Before propensity matching		After propensity matching	Before propensity matching		After propensity matching
	AF	No AF	P value	AF	No AF	P value	AF	No AF	P value
Demographics									
Age	38.8 ± 6.4	36.5 ± 6.8	<.001	38.8 ± 6.4	38.8 ± 6.4	.94	71.9 ± 5.7	69.0 ± 6.2	<.001
White	53.8%	48.6%	<.001	53.8%	54.2%	.081	70.3%	58.5%	<.001
Men	63.6%	48.0%	<.001	63.4%	63.5%	.675	55.0%	44.6%	<.001
Comorbidities									
Obesity	26.3%	10.7%	<.001	25.9%	25.9%	.94	12.7%	2.0%	<.001
Nicotine use	18.6%	7.0%	<.001	18.2%	18.5%	.143	6.2%	1.6%	<.001
Alcohol use	7.4%	2.3%	<.001	7.2%	7.4%	.107	2.1%	0.5%	<.001
Alcohol use disorder									
Hormone replacement	1.0%	0.2%	<.001	0.9%	0.8%	.17	1.0%	0.2%	<.001
Medications									
Antihyperlipidemic	21.0%	4.7%	<.001	20.6%	20.2%	.11	35.2%	13.4%	<.001
Aspirin	27.0%	4.3%	<.001	26.6%	26.7%	.892	27.6%	8.0%	<.001
Laboratory values									
A1c	6.3 ± 2.0 (32.1% of cohort)	6.4 ± 2.1 (14.5% of cohort)	.085	6.3 ± 2.2 (31.7% of cohort)	6.2 ± 1.9 (31.5% of cohort)	<.001	6.5 ± 1.7 (25.5% of cohort)	6.6 ± 1.8 (9.4% of cohort)	<.001

AF = atrial fibrillation.

propensity matching, there were 510,308 patients in both groups. The mean age in both groups was 58.2 ± 6.4 .

In the 70–85 age group, our query resulted in 976,094 patients with AF and 4,995,924 patients without AF. After propensity matching, there were 882,729 patients in both groups. The mean age in both groups was 71.7 ± 6 .

Rhythm control and anticoagulation

We examined rhythm control and anticoagulation strategies within the AF cohort over the follow-up period before propensity score matching. Among patients aged 30–50 years, 17% received amiodarone, followed by 5% flecainide, 3% sotalol, and approximately 1% each for dofetilide, propafenone, and dronedarone. In the 50–70 age group, 23% were treated with amiodarone, with similar patterns for other agents. Among those aged 70–85 years, 22% received amiodarone, whereas flecainide, sotalol, dofetilide, and dronedarone each accounted for 2%–3% of use.

With regard to oral anticoagulation, apixaban was the most prescribed agent across all age groups (26% in ages 30–50 years, 34% in ages 50–70 years, and 35% in ages 70–85 years). Warfarin use ranged from 11% to 17%, whereas rivaroxaban use was slightly lower (9%–13%), and dabigatran use remained below 3% across all groups.

Pulmonary vein isolation was performed in 4% of patients aged 30–50 years, 6% aged 50–70 years, and 3% aged 70–85 years (see [Supplemental Table 2](#) for a summary of rhythm control strategies and anticoagulant use).

Outcomes

Age 30–50 years

In the age 30–50 age group, the AF cohort had a mean follow-up of 1029 ± 1115 days with a median of 659 days (interquartile range [IQR] 1398) compared with 1032 ± 1143 days and a median of 646 days (IQR 1437) in the non-AF cohort.

AF was associated with significant increases in cancer risk across several cancer types, although the absolute risk differences were smaller than older age groups. The risk of any cancer was higher in individuals with AF (1.17% vs 0.39%; risk difference 0.78%; $P < .001$). The RR was 2.99 (95% confidence interval [CI] 2.60–3.44).

Patients with AF had significantly higher risks of multiple cancers types, including colorectal (RR 3.43; 95% CI 1.89–6.22; $P < .001$), breast (RR 2.00; 95% CI 1.29–3.10; $P = .002$), lung (RR 3.00; 95% CI 1.47–6.14; $P = .002$), hepatobiliary (RR 3.64; 95% CI 1.87–7.09; $P < .001$), renal (RR 3.60; 95% CI 2.03–6.38; $P < .001$), thyroid (RR 2.59; 95% CI 1.58–4.24; $P < .001$), non-Hodgkin's lymphoma (RR 3.26; 95% CI 1.95–5.46; $P < .001$), and leukemia (RR 3.88; 95% CI 2.28–6.62; $P < .001$).

Several cancers showed no statistically significant association with AF in this age group, including prostate, bladder, ovarian, uterine, brain, pancreatic, esophageal, Hodgkin's lymphoma, and multiple myeloma ([Figure 1A](#), [Supplemental Table 3](#)).

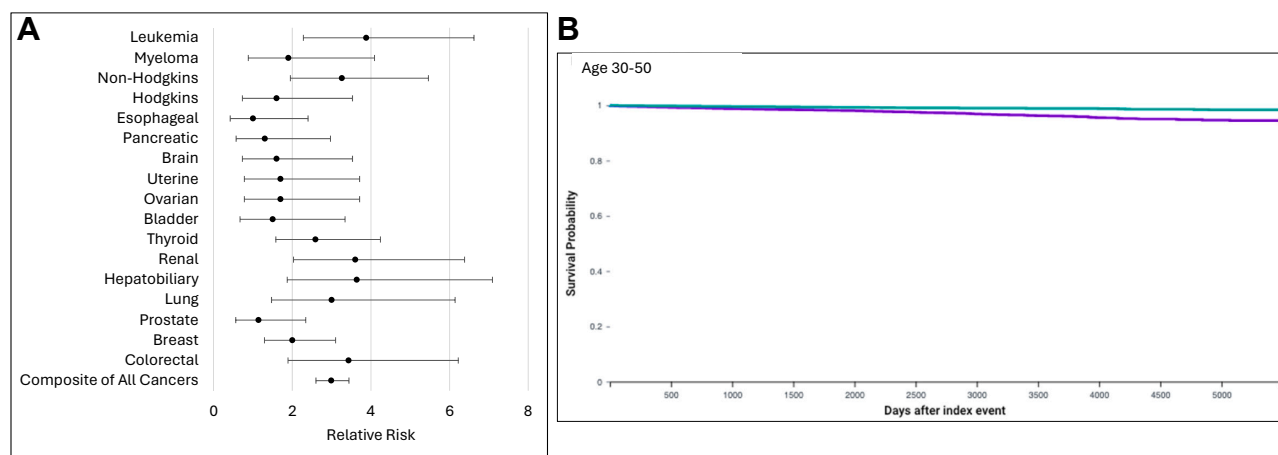


Figure 1

Risk of cancer with atrial fibrillation, age 30–50 years. A: Forest plot of the relative risk of cancer types in the 30–50 age group. B: Kaplan–Meier curve of freedom for all-cause malignancy in the 30–50 age group. AF = atrial fibrillation.

Freedom from cancer at 15 years was 94.45% in the AF group vs 98.34% in the no-AF group ($P < .001$; HR 2.96; 95% CI 2.57–3.40) (Figure 1B).

Age 50–70 years

In the 50–70 age group, the AF cohort had a mean of 1088 ± 1168 days and a median of 702 days (IQR 1517), whereas the non-AF group had a mean of 1442 ± 1495 days and a median of 954 days (IQR 2216).

The risk of any cancer was higher in individuals with AF (1.72% vs 0.96%; risk difference 0.76%; $P < .001$). The RR was 1.79 (95% CI 1.73–1.85).

Patients with AF exhibited significantly increased risks of all cancer types, including colorectal (RR 2.22; 95% CI 1.94–2.54; $P < .001$), breast (RR 1.49; 95% CI 1.34–1.66; $P < .001$), prostate (RR 1.31; 95% CI 1.21–1.42; $P < .001$), lung (RR 1.96; 95% CI 1.79–2.16; $P < .001$), hepatobiliary (RR 1.89; 95% CI 1.63–2.18; $P < .001$), renal (RR 2.31; 95% CI 1.98–2.71; $P < .001$), thyroid (RR 2.38; 95% CI 1.95–2.90; $P < .001$), bladder (RR 1.52; 95% CI 1.27–1.83; $P < .001$),

ovarian (RR 1.99; 95% CI 1.49–2.65; $P < .001$), uterine (RR 2.37; 95% CI 1.88–2.99; $P < .001$), brain (RR 1.51; 95% CI 1.16–1.95; $P = .002$), pancreatic (RR 1.91; 95% CI 1.58–2.31; $P < .001$), esophageal (RR 2.64; 95% CI 2.02–3.46; $P < .001$), Hodgkin's lymphoma (RR 4.44; 95% CI 2.67–7.41; $P < .001$), non-Hodgkin's lymphoma (RR 2.36; 95% CI 1.99–2.80; $P < .001$), multiple myeloma (RR 2.44; 95% CI 1.97–3.03; $P < .001$), and leukemia (RR 2.05; 95% CI 1.71–2.45; $P < .001$) (Figure 2A).

No cancers in this age group showed a nonsignificant association with AF.

Freedom from cancer at 15 years was 92.08% in the AF group vs 95.63% in the no-AF group ($P < .001$; HR 1.84; 95% CI 1.78–1.91) (Figure 2B).

Age 70–85 years

In the 70–85 age group, mean follow-up was 1135 ± 1210 days with a median of 736 days (IQR 1653) in the AF group and 1493 ± 1529 days with a median of 1004 days (IQR 2338) in the non-AF group.

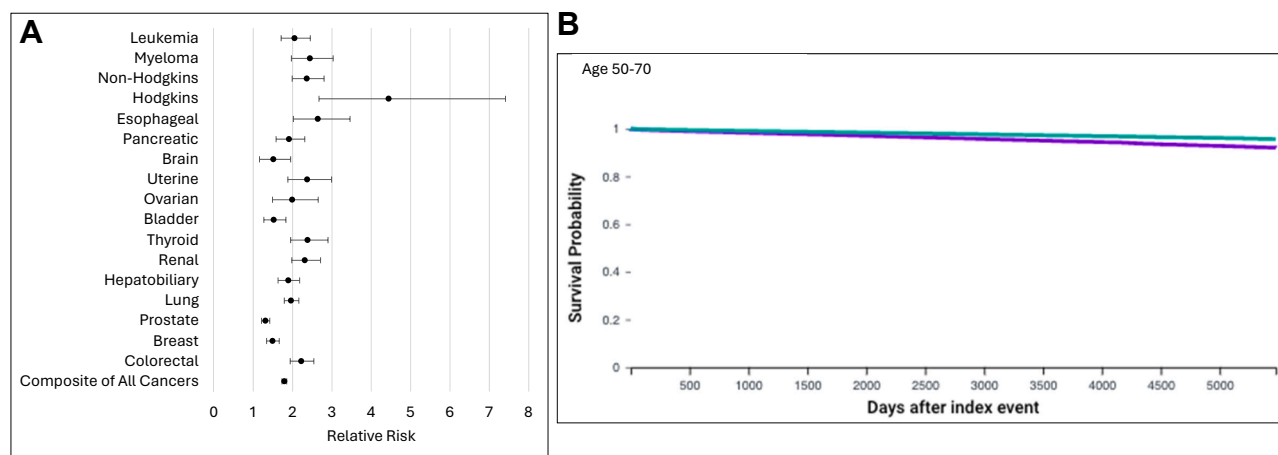
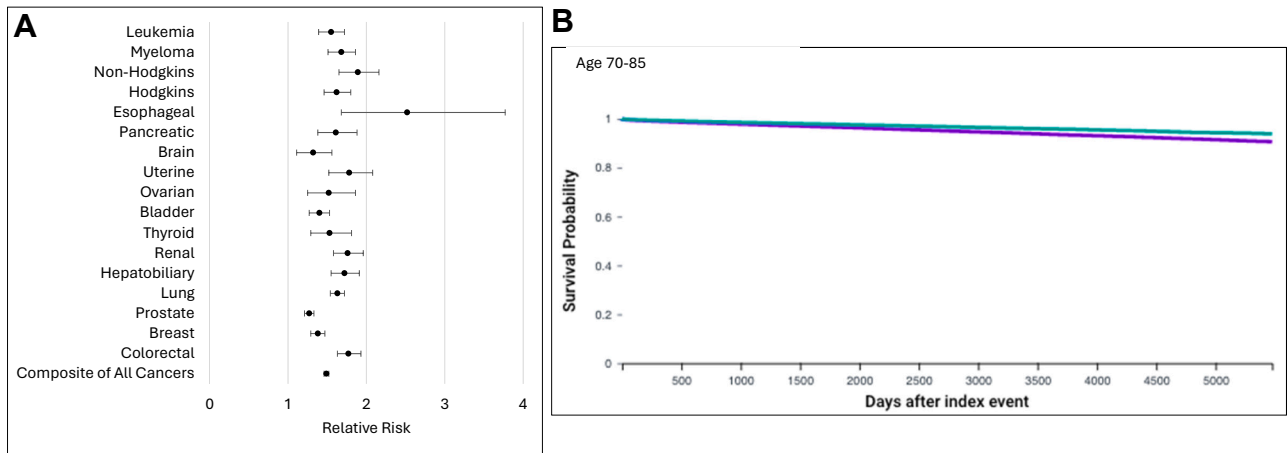


Figure 2

Risk of cancer with AF, age 50–70 years. A: Forest plot of the relative risk of cancer types in the 50–70 age group. B: Kaplan–Meier curve of freedom for all-cause malignancy in the 50–70 age group. AF = atrial fibrillation.

**Figure 3**

Risk of cancer with AF, age 70–85 years. A: Forest plot of the relative risk of cancer types in the 70–85 age group. B: Kaplan–Meier curve of freedom for all-cause malignancy in the 70–85 age group. AF = atrial fibrillation.

In individuals aged 70–85 years, AF remained significantly associated with cancer risk, but the RRs were generally lower than younger groups. The risk of any cancer was higher in individuals with AF (2.20% vs 1.50%; risk difference 0.7%; $P < .001$). The RR was 1.49 (95% CI 1.46–1.52).

In this age group, patients with AF exhibited significantly increased risks of all cancer types, including colorectal (RR 1.77; 95% CI 1.63–1.93; $P < .001$), breast (RR 1.38; 95% CI 1.29–1.48; $P < .001$), prostate (RR 1.27; 95% CI 1.21–1.33; $P < .001$), lung (RR 1.63; 95% CI 1.54–1.72; $P < .001$), hepatobiliary (RR 1.72; 95% CI 1.55–1.91; $P < .001$), renal (RR 1.76; 95% CI 1.58–1.96; $P < .001$), thyroid (RR 1.53; 95% CI 1.29–1.81; $P < .001$), bladder (RR 1.40; 95% CI 1.27–1.53; $P < .001$), ovarian (RR 1.52; 95% CI 1.25–1.86; $P < .001$), uterine (RR 1.78; 95% CI 1.52–2.08; $P < .001$), brain (RR 1.32; 95% CI 1.11–1.56; $P < .001$), pancreatic (RR 1.55; 95% CI 1.39–1.72; $P < .001$), esophageal (RR 1.61; 95% CI 1.38–1.88; $P < .001$), Hodgkin's lymphoma (RR 2.52; 95% CI 1.68–3.77; $P < .001$), non-Hodgkin's lymphoma (RR 1.62; 95% CI 1.46–1.80; $P < .001$), multiple myeloma (RR 1.89; 95% CI 1.65–2.16; $P < .001$), and leukemia (RR 1.68; 95% CI 1.51–1.87; $P < .001$) (Figure 3A).

Freedom from cancer at 15 years was 90.63% in the AF group and 93.84% in the no-AF group ($P < .001$; HR 1.53; 95% CI 1.49–1.56) (Figure 3B).

Sensitivity analysis 1: Cancer risk within the first 3 months after AF diagnosis

A sensitivity analysis, using propensity score-matched data, evaluated the short-term impact of AF on cancer risk at 3 months across age cohorts.

In the 30–50 age group, patients with AF had a cancer risk of 0.25% compared with 0.08% in the no-AF group, with a risk difference of 0.17%. The risk ratio was 3.02 (95% CI 2.23–4.08). Cancer-free survival in the AF group was lower (99.71%) than the non-AF group (99.90%), with an HR of 2.93 (95% CI 2.17–3.96; $P < .001$).

In the 50–70 age group, patients with AF had a cancer risk of 0.39% compared with 0.19% in the no-AF group, with a risk difference of 0.20%. The risk ratio was 2.10 (95% CI 1.95–2.26). Cancer-free survival in the AF group was lower (99.56%) than the no-AF group (99.78%), with an HR of 2.04 (95% CI 1.89–2.20; $P < .001$).

In the 70–85 age group, patients with AF had a cancer risk of 0.51% compared with 0.31% in the no-AF group, with a risk difference of 0.20%. The risk ratio was 1.66 (95% CI 1.58–1.74). Cancer-free survival in the AF group was lower (99.41%) than the no-AF group (99.63%), with an HR of 1.61 (95% CI 1.54–1.69; $P < .001$).

Sensitivity analysis 2: Cancer risk 1 year after AF diagnosis

To address concerns regarding reverse causation, a sensitivity analysis was performed, assessing the incidence of cancer 1 year after an AF diagnosis. This approach aimed to mitigate the likelihood that preexisting but undiagnosed malignancy contributed to AF onset.

In the 30–50 age group, patients with AF had a composite cancer risk of 0.81% compared with 0.29% in the no-AF group, with a risk difference of 0.52%. The risk ratio was 2.81 (95% CI 2.39–3.30). Cancer-free survival in the AF group was lower (95.07%) than the non-AF group (97.72%), with an HR of 2.83 (95% CI 2.41–3.33; $P < .001$).

In the 50–70 age group, patients with AF had a composite cancer risk of 1.23% compared with 0.68% in the no-AF group, with a risk difference of 0.55%. The risk ratio was 1.82 (95% CI 1.75–1.90). Cancer-free survival in the AF group was lower (92.74%) than the no-AF group (96.38%), with an HR of 1.92 (95% CI 1.84–2.00; $P < .001$).

In the 70–85 age group, patients with AF had a composite cancer risk of 1.61% compared with 1.09% in the no-AF group, with a risk difference of 0.52%. The risk ratio was 1.48 (95% CI 1.45–1.52). Cancer-free survival in the AF group was lower (91.58%) than the no-AF group (94.44%), with an HR of 1.55 (95% CI 1.51–1.59; $P < .001$).

Table 2 Multivariable Cox regression model for all-cause malignancy

Covariate	30–50 y AF: 5760 patients No AF: 497,839 patients		50–70 y AF: 62,932 patients No AF: 1,903,597 patients		70–85 y AF: 171,705 patients No AF: 1,765,671 patients	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Cohort 1 vs 2	1.781 (1.554–2.042)	<.0001	1.185 (1.149–1.222)	<.0001	1.157 (1.139–1.175)	<.0001
Demographics						
Age at index	1.057 (1.053–1.061)	<.0001	1.068 (1.067–1.069)	<.0001	1.045 (1.044–1.046)	<.0001
Men	0.632 (0.608–0.658)	<.0001	0.994 (0.983–1.005)	.2764	1.307 (1.296–1.318)	<.0001
White	1.062 (1.011–1.115)	.0157	1.099 (1.083–1.116)	<.0001	1.057 (1.045–1.069)	<.0001
AA race	0.916 (0.866–0.969)	.0024	1.133 (1.113–1.154)	<.0001	1.128 (1.111–1.146)	<.0001
Comorbidities						
ESRD	2.518 (2.272–2.790)	<.0001	1.498 (1.431–1.569)	<.0001	1.053 (1.004–1.104)	.0346
COPD	1.408 (1.139–1.740)	.0015	1.513 (1.471–1.555)	<.0001	1.465 (1.438–1.491)	<.0001
Fatty liver	1.348 (1.151–1.579)	.0002	1.244 (1.183–1.307)	<.0001	1.190 (1.136–1.245)	<.0001
Systolic heart failure	1.291 (1.026–1.625)	.0292	1.044 (0.978–1.115)	.1964	0.977 (0.933–1.023)	.3148
Cerebral infarction	1.214 (0.992–1.485)	.06	0.983 (0.938–1.030)	.4665	0.893 (0.865–0.921)	<.0001
CAD	1.185 (1.056–1.331)	.0039	0.940 (0.920–0.960)	<.0001	0.917 (0.906–0.929)	<.0001
Alcohol abuse	1.026 (0.879–1.199)	.7415	1.259 (1.211–1.309)	<.0001	1.211 (1.161–1.262)	<.0001
Hypertension	0.949 (0.888–1.014)	.1201	0.942 (0.928–0.957)	<.0001	0.967 (0.957–0.978)	<.0001
T2DM	0.936 (0.878–0.998)	.0425	0.960 (0.947–0.974)	<.0001	0.946 (0.937–0.956)	<.0001
Tobacco use	0.886 (0.685–1.144)	.3522	1.191 (1.120–1.267)	<.0001	1.392 (1.312–1.477)	<.0001
Obesity	0.989 (0.930–1.051)	.7175	0.986 (0.965–1.007)	.1913	1.023 (1.004–1.042)	.0184
Rhythm control						
Amiodarone	0.777 (0.494–1.223)	.2761	0.965 (0.878–1.061)	.4617	0.889 (0.842–0.939)	<.0001
Sotalol	0.568 (0.212–1.524)	.2615	0.884 (0.722–1.082)	.2307	0.837 (0.759–0.923)	.0004
Flecainide	-	-	0.742 (0.604–0.911)	.0044	0.817 (0.732–0.913)	.0003
Dronedarone	-	-	0.777 (0.577–1.047)	.0972	0.836 (0.734–0.953)	.0071
Dofetilide	-	-	0.828 (0.611–1.123)	.2245	0.929 (0.807–1.069)	.3039
EP ablation	-	-	0.424 (0.211–0.852)	.0159	0.873 (0.656–1.161)	.3506
Anticoagulation						
Warfarin	1.361 (1.148–1.614)	.0004	1.023 (0.975–1.073)	.3575	0.932 (0.906–0.959)	<.0001
Apixaban	0.914 (0.228–3.666)	.8995	1.175 (0.951–1.452)	.136	1.011 (0.904–1.129)	.8515
Rivaroxaban	0.876 (0.454–1.690)	.6931	1.057 (0.927–1.205)	.4048	1.012 (0.945–1.084)	.7329

For the age 30–50 age groups, flecainide, dofetilide, dronedarone, and EP ablation were included in the preliminary model but subsequently removed owing to extremely low counts. These variables showed unstable estimates (eg, HR <0.001; 95% CI 0–0; $P = 1$), indicating a lack of informative data for modeling.

AA = African American; AF = atrial fibrillation; CAD = coronary artery disease; CI = confidence interval; COPD = chronic obstructive pulmonary disease; EP = electrophysiology; ESRD = end-stage renal disease; HR = hazard ratio; T2DM = type 2 diabetes mellitus.

Sensitivity analysis 3: Cancer risk in paroxysmal and persistent AF vs no AF

We evaluated cancer risk by AF subtype using matched cohorts of patients with paroxysmal or persistent AF compared with non-AF controls. Persistent AF consistently demonstrated a higher RR of cancer than paroxysmal AF across all age groups. In the 30–50 age group, RRs were 2.01 (95% CI 1.66–2.42) for paroxysmal AF and 3.59 (95% CI 2.38–5.41) for persistent AF. Among patients aged 50–70 years, RRs were 1.96 (95% CI 1.87–2.01) and 2.84 (95% CI 2.64–3.05), respectively. In the 70–85 age group, paroxysmal AF had an RR of 1.95 (95% CI 1.90–2.01) and persistent AF had an RR of 2.05 (95% CI 1.75–2.39) (see [Supplemental Table 4](#)).

Sensitivity analysis 4: Cancer risk with multivariable Cox proportional hazards analysis

To further evaluate the independent association between AF and incident cancer, we constructed age-stratified multivariable Cox proportional hazards models incorporating a comprehensive set of covariates. The analysis was restricted

to patients with index diagnoses between June 19, 2010, and June 19, 2015, to allow for at least 10 years of follow-up while maintaining adequate statistical power for covariate adjustment (see [Table 2](#)).

Across all age groups, AF remained independently associated with an increased cancer risk compared with the non-AF cohort. The strength of association was highest among patients aged 30–50 years (HR 1.781; 95% CI 1.554–2.042; $P < .0001$), followed by the 50–70 (HR 1.185; 95% CI 1.149–1.222; $P < .0001$) and 70–85 age groups (HR 1.157; 95% CI 1.139–1.175; $P < .0001$).

In addition to AF status, several other covariates were independently associated with cancer incidence. Notably, warfarin use was associated with an increased cancer risk in the youngest cohort (30–50), but not in the higher age groups. Apixaban, rivaroxaban, and dabigatran were not consistently associated with cancer risk across age groups.

Among rhythm control strategies, catheter ablation was associated with a significantly lower cancer risk in the 50–70 age group (HR 0.424; 95% CI 0.211–0.852; $P = .0159$), although not in the other age strata. Select antiarrhythmic drugs, including flecainide, sotalol, and dronedarone, were associated

with a lower cancer risk in older patients, whereas amiodarone showed a modest protective association only in the 70–85 age group (HR 0.889; 95% CI 0.842–0.939; $P < .0001$).

Sensitivity analysis 5: Cancer risk in patients with low-risk AF without prespecified comorbidity requirements

To evaluate whether the association between AF and incident cancer persisted independent of baseline comorbidities, we constructed a low-risk cohort without any prespecified comorbidity requirements. To ensure adequate data quality and limit sample size for adequate analysis, inclusion was restricted to patients with ≥ 2 outpatient visits and ≥ 1 documented 12-lead electrocardiogram. We then performed more extensive propensity matching between patients with AF and without AF to balance baseline demographics and clinical characteristics. Baseline characteristics are presented in Table 3.

In the 30–50 age group, cancer occurred in 2.65% of patients with AF vs 1.83% of patients without AF (RR 1.45; 95% CI 1.32–1.59); cancer-free survival was 92.0% vs 94.1% (log-rank $P < .001$; HR 1.30; 95% CI 1.18–1.42) (Figure 4).

In the 50–70 age group, cancer occurred in 7.85% of patients with AF vs 6.50% of patients without AF (RR 1.21; 95% CI 1.19–1.23); cancer-free survival was 78.1% vs 81.0% (log-rank $P < .001$; HR 1.09; 95% CI 1.07–1.11).

In the 70–85 age group, cancer occurred in 13.51% of patients with AF vs 11.06% of patients without AF (RR 1.22; 95% CI 1.21–1.23); cancer-free survival was 67.1% vs 70.7% (log-rank $P < .001$; HR 1.09; 95% CI 1.08–1.10).

Discussion

In this large, real-world observational study leveraging the TriNetX research network, we found a consistent and robust association between AF and incident cancer across a broad spectrum of analyses. The increased cancer risk among patients with AF was evident in both risk ratio comparisons and Kaplan–Meier survival analyses across all age strata. Importantly, the association remained significant in multiple sensitivity analyses designed to address potential sources of bias, including restricting cancers to those diagnosed within 3 months of AF diagnosis, evaluating cancers diagnosed after 1 year to minimize reverse causation, stratifying by AF subtype (paroxysmal vs persistent), limiting analyses to low-risk patients without prespecified comorbidity requirements, and adjusting with multivariable Cox proportional hazards models incorporating more comprehensive covariates. Across all approaches, AF was independently associated with a heightened risk of cancer, with the strongest RRs observed in the youngest age group (30–50 years). These findings suggest that AF may serve as an early indicator, or potentially a contributing factor, in cancer pathogenesis, particularly among younger adults.

Beyond the overall association between AF and cancer risk, several important trends emerged. Although the absolute incidence of cancer increased with age, the RR associated with AF was highest in the youngest cohort and

Table 3 Baseline characteristics—cancer risk in patients with low-risk AF without prespecified comorbidity requirements (sensitivity analysis 5)

Variable	Age 30–50 y						Age 50–70 y						Age 70–85 y					
	Before propensity match			After propensity match			Before propensity match			After propensity match			Before propensity match			After propensity match		
	AF	No AF	P value	AF	No AF	P value	AF	No AF	P value	AF	No AF	P value	AF	No AF	P value	AF	No AF	P value
Age at index (y)	37.3 ± 6.9	34.5 ± 7.3	<.001	37.3 ± 6.9	36.3 ± 6.9	<.001	57.5 ± 6.6	54.2 ± 7.2	<.001	57.5 ± 6.6	57.5 ± 6.6	.005	70.9 ± 5.9	68.9 ± 6.3	<.001	70.9 ± 5.9	70.9 ± 5.9	.446
White (%)	65.7	64.1	<.001	65.8	65.9	.729	75.9	70.4	<.001	75.9	76.3	.001	83.4	76.3	<.001	83.4	83.6	<.001
Men (%)	64.3	39.0	<.001	64.3	64.6	.324	64.6	45.2	<.001	64.5	65.1	<.001	57.6	44.4	<.001	57.3	57.9	<.001
End-stage renal disease (%)	4.3	0.9	<.001	4.2	4.1	.389	4.4	1.3	<.001	4.1	3.8	<.001	2.7	1.2	<.001	2.4	2.3	<.001
COPD (%)	3.1	0.8	<.001	3.0	2.8	.084	10.8	4.9	<.001	10.5	10.1	<.001	12.0	7.5	<.001	11.5	11.0	<.001
Fatty liver (%)	4.7	3.0	<.001	4.7	4.5	.220	5.2	3.7	<.001	5.1	4.6	<.001	3.5	2.8	<.001	3.4	3.1	<.001
Systolic heart failure (%)	7.7	0.6	<.001	7.6	7.6	.907	7.3	1.2	<.001	6.8	6.8	.688	5.2	1.3	<.001	4.3	4.1	<.001
Cerebral infarction (%)	4.0	0.9	<.001	3.9	4.0	.438	5.8	2.3	<.001	5.6	5.5	.132	6.4	3.4	<.001	6.1	6.0	.005
Chronic ischemic heart disease (%)	8.9	1.3	<.001	8.7	8.6	.444	20.8	7.3	<.001	20.4	20.2	.010	26.2	14.1	<.001	25.3	25.0	<.001
Alcohol-related disorders (%)	5.9	4.9	<.001	5.9	5.8	.439	6.4	4.8	<.001	6.3	6.0	<.001	3.1	2.5	<.001	3.0	2.8	<.001
Hypertension (%)	31.2	17.9	<.001	31.1	30.9	.429	48.4	39.4	<.001	48.2	47.3	<.001	52.7	51.5	<.001	52.2	50.9	<.001
Type 2 diabetes (%)	12.5	7.1	<.001	12.4	12.2	.525	23.5	16.9	<.001	23.2	22.7	<.001	24.7	21.9	<.001	24.3	23.7	<.001
Nicotine dependence (%)	17.2	16.3	<.001	17.1	16.9	.357	17.5	15.5	<.001	17.4	16.7	<.001	9.8	9.2	<.001	9.6	9.1	<.001
Overweight/obesity (%)	24.2	19.6	<.001	24.2	23.8	.298	25.3	18.9	<.001	25.1	24.3	<.001	19.4	14.2	<.001	18.9	18.2	<.001

AF = atrial fibrillation; COPD = chronic obstructive pulmonary disease.

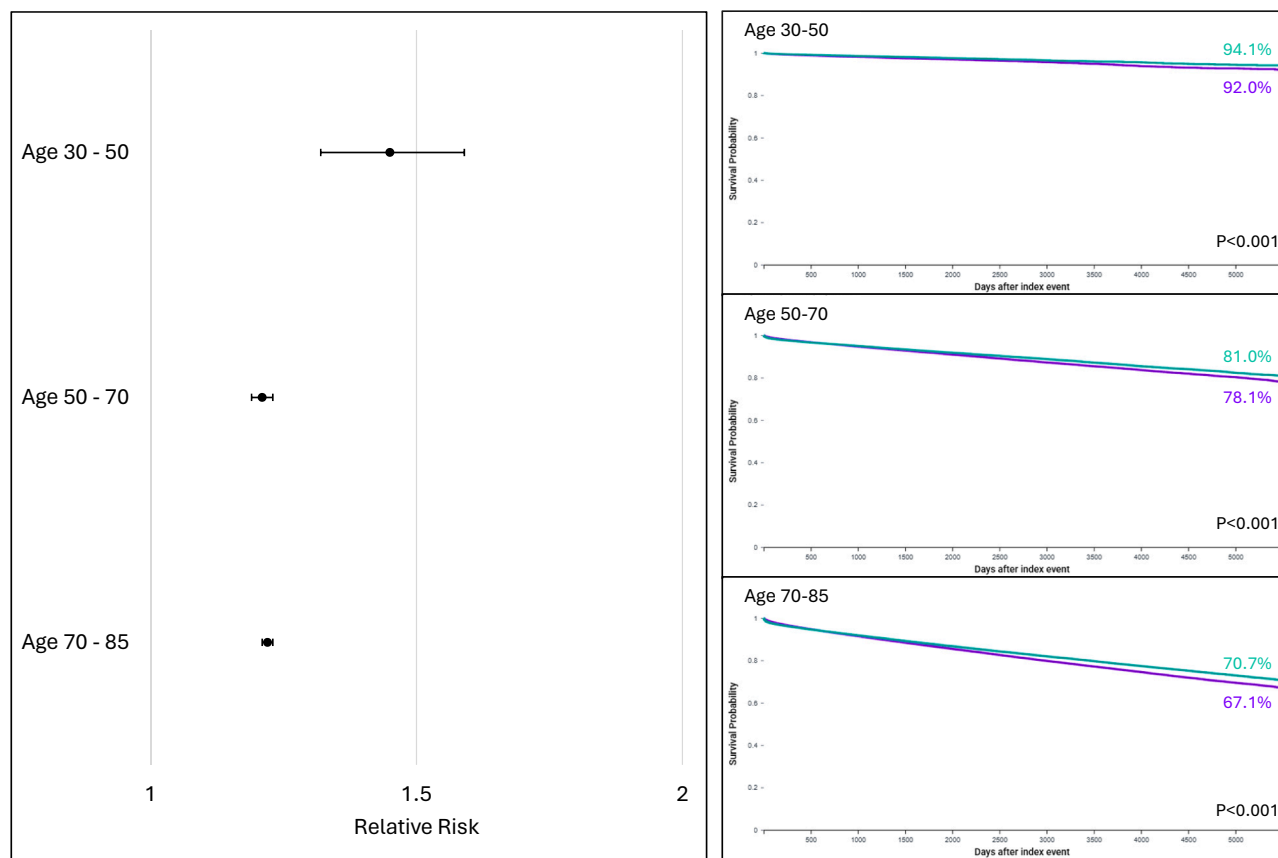


Figure 4 Cancer risk in patients with low-risk AF without prespecified comorbidity requirements (sensitivity analysis 5). Relative risk of all-cause malignancy across age groups (left panel) and Kaplan–Meier survival analysis across age groups (right panels).

progressively declined in older age groups. This pattern suggests a possible age-related interaction, whereby AF may represent a stronger independent marker of cancer risk in younger individuals, who otherwise have lower baseline malignancy rates. In contrast, it is also possible that younger individuals with AF represent a clinically distinct and sicker subgroup with higher comorbidity burden or health complexity not fully captured by available data. These factors may contribute to both AF and increased cancer risk and may partially explain the stronger association observed in this age group. In contrast, the elevated cancer burden in older adults may dilute the relative impact of AF. Specific malignancies demonstrated particularly strong and consistent associations with AF across all age groups, pointing toward potential shared pathophysiological mechanisms. Esophageal cancer, notably, was the most strongly associated solid tumor in older patients. Although the underlying mechanisms are uncertain, shared behavioral risk factors such as alcohol use and possible anatomical interactions have been proposed.¹²

In a sensitivity analysis restricted to AF subtypes, both paroxysmal and persistent AF were independently associated with an increased cancer risk compared with controls without AF, with persistent AF demonstrating consistently higher RRs across all age groups. Persistent AF is more often

associated with advanced atrial structural changes, sustained inflammatory activation, and greater comorbidity burden, all of which may contribute to a biologic environment conducive to malignancy. In addition, persistent AF may prompt more intensive clinical monitoring, potentially increasing the likelihood of cancer detection. These findings suggest that AF subtype may carry prognostic relevance when evaluating long-term cancer risk.

In our multivariable Cox models, we found that several rhythm control and anticoagulation strategies were independently associated with cancer risk, warranting further consideration of how AF management may influence long-term oncologic outcomes. Warfarin use was associated with an increased cancer risk in younger adults, which may reflect reverse causality, given that malignancies can manifest with bleeding complications that lead to earlier detection in anticoagulated patients. Conversely, certain antiarrhythmic drugs, particularly flecainide and dronedarone, were associated with a lower cancer risk, especially in older age groups. However, these agents are typically prescribed to healthier patients without significant structural heart disease, which may introduce confounding by indication. Similarly, catheter ablation was associated with reduced cancer risk in the 50–70 age group, although this may reflect selection bias, given

that patients chosen for ablation may be healthier or have better health care engagement. These findings suggest that observed associations between AF treatments and cancer risk may be influenced more by underlying patient characteristics and surveillance intensity than by direct pharmacologic or procedural effects.

The association between AF and cancer likely arises from a complex interplay of genetic, environmental, metabolic, and inflammatory factors. Cancer itself may predispose individuals to AF through systemic inflammation, adverse effects of cytotoxic drug therapy, pain and stress, autonomic dysfunction, electrolyte abnormalities, infections, or direct insult to the atrial myocytes via tumor growth or metastasis.^{5–7} Both conditions share common risk factors, including hypertension, diabetes, coronary artery disease, smoking, alcohol use, and obesity, which may contribute to a heightened baseline susceptibility.^{4,13} Emerging research indicates that common genetic pathways contribute to both cardiovascular disease and cancer.^{14–16} This genetic overlap could explain the observed association between these 2 conditions. Another potential explanation for this bidirectional relationship is increased health care utilization after an AF diagnosis, leading to more frequent diagnostic testing and incidental cancer detection. Finally, anticoagulation therapy, commonly initiated in patients with AF, may unmask occult malignancies by triggering malignancy-related bleeding events that prompt further investigation.¹⁷

Our findings align with previous studies examining the association between AF and cancer. Ostenfeld et al¹⁰ compared cancer incidence in patients with AF with the expected cancer incidence in the general Danish population, reporting an increased RR of cancer, particularly within the first 3 months of AF diagnosis. Our results align with those of Ostenfeld et al,¹⁰ particularly regarding the association of non-Hodgkin's lymphoma and other hematologic malignancies. Similarly, Vinter et al¹¹ observed a higher likelihood of metastatic cancer at the time of cancer diagnosis in patients with AF, with an increased risk of cancer within 90 days of AF onset. Unlike our study, these analyses did not incorporate propensity score matching or extended follow-up. Conen et al¹⁸ further demonstrated that the risk of cancer diagnosis was highest in the first 90 days after AF diagnosis but remained elevated up to 1 year later in women enrolled in the Women's Health Study. In addition, a case-control study found that AF events were associated with an approximately 1.85-fold increased risk of malignancy, suggesting that AF may serve as an early indicator of cancer.¹⁹

Strengths

One of the major strengths of our study is the use of a large national cohort database, which enabled the inclusion of a substantial number of patients and age-stratified analyses. This approach allowed us to identify a heightened cancer

risk associated with AF in younger individuals. In addition, propensity score matching improved the comparability of study groups, reducing potential confounding and strengthening the validity of our findings. Finally, our extensive sensitivity analyses add robustness to our results.

Limitations

Despite its strengths, this study has several limitations. As a retrospective observational study, it is susceptible to selection bias, confounding, and potential inaccuracies in electronic medical record data. The reliance on International Classification of Diseases coding introduces the possibility of misclassification or missing diagnoses, which may affect the precision of our findings. Importantly, given that this was a retrospective observational study, our findings demonstrate association rather than causation.

Despite the use of propensity score matching, the possibility of unmeasured or unknown confounding remains. Variables such as genetic risk, environmental exposures, or health care access, which were not available in the dataset, may influence the observed associations. In addition, although alcohol use was included in propensity matching, it was categorized as a binary variable rather than a quantified measure, potentially reducing its accuracy.

Reverse causation is another major limitation, given that undiagnosed malignancies could contribute to AF onset rather than AF predisposing individuals to cancer. Several mechanisms, including malignant pericardial effusions, hyperdynamic circulation, systemic inflammation, sepsis, electrolyte disturbances, and paraneoplastic syndromes, may drive this association, particularly in patients with hematologic malignancies or advanced-stage cancers. We attempted to address this issue through sensitivity analyses.

Conclusion

Our study reinforces previous findings of an association between AF and incident cancer, with a stronger correlation observed in younger patients. However, the possibility of reverse causation, unmeasured confounders, and medication-related biases limits the strength of causal inferences. Future prospective studies are needed to elucidate the mechanisms underlying this association and explore the complex genetic, metabolic, inflammatory, and cellular pathways linking AF and cancer.

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Ethics Statement: This study used data from the TriNetX Research network (TriNetX, Inc, Cambridge, MA). TriNetX is a global federated health research network providing access to electronic medical records (diagnoses, procedures, medications, laboratory values, genomic information) across large health care organizations. As a federated network, TriNetX received a waiver from the Western Institutional Review Board given that only aggregated counts and statistical summaries of deidentified information were received, no protected health information was received, and no study-specific activities were performed in retrospective analyses.

Appendix

Supplementary data

Supplementary data associated with this article can be found in the online version at <https://doi.org/10.1016/j.hrthm.2025.10.040>.

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