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SERMENT D'HIPPOCRATE

En présence des Maîtres de cette Faculté,
de mes chers condisciples
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je promets et je jure d'être fidèle aux lois de l'honneur et de la probité dans l'exercice de la Médecine.
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ABSTRACT

Background. An association between cancer and atrial fibrillation (AF) has been evoked and AF may affect the prognosis of malignant disease and vice-versa. **Our aim was to investigate the risk of developing AF for different locations of cancer, the risk of ischemic stroke in people with AF and cancer and to evaluate the predictive values of the risk stratification scores.**

Methods. This French cohort study was based on the national database PMSI. We included 3,381,472 patients seen in the French hospitals in 2013 and compared the incidence of AF for different cancer types. We then studied the incidence of ischemic stroke in a second population of patients with AF seen from 2010 to 2019, for each cancer type compared to those with no cancer.

Results. Of the 3,381,472 patients, 421,829 had cancer with the most common being breast, prostatic, colorectal and lung cancer. The incidence of AF was higher in the group with a history of cancer (9.97% vs 9.63%, p<0.001). Patients with lung cancer were at highest risk of AF (HR of 1.673 [CI 1.621-1.725, p<0.001]), followed by hematologic cancers, uterine and liver cancer. There was no statistical difference for renal, gastric and pancreatic cancers. Patients with prostatic, bladder, colorectal, breast and ovarian cancers were less likely to develop AF. In the 2,435,541 patients with AF, the risk of ischemic stroke was lower in patients with a history of cancer. The CHA_2DS_2-VASc score was associated with thromboembolic risk in AF patients with cancer but its predictive value was lower than in those with no cancer. The predictive performance of HASBLED score was good.

Conclusions. Cancer patients are at higher risk of developing AF and the risk varies according to cancer types. The incidence of stroke was lower in the group of patients with AF. The predictive values of the CHA_2DS_2VASc and HASBLED scores were good but should be used with caution.

Keywords. Atrial fibrillation, cancer, thromboembolism, ischemic stroke, onco-cardiology

ABBREVIATIONS

AF : Atrial fibrillation

CI : Confidence interval

ICD : International Classification of Disease

PMSI : Programme de Médicalisation des Systèmes d'Information

IR : Incidence rates

IQR : Interquartile range

HR : Hazard ratio

SD : Standard deviation

AUC : Area under curve

ROC : Receiver operating characteristic

FU : Follow up

COPD : Chronic obstructive pulmonary disease

CABG : Coronary artery bypass graft

PCI : Percutaneous coronary intervention

ICD : Implantable cardioverter defibrillator

TABLE DES MATIERES

I. INTRODUCTION

Onco-cardiology is a new medical field linking two medical specialties and has gained a lot of interest these past decades. Cancer is a leading cause of death worldwide accounting for nearly 10 million deaths in 2020(1) and the first cause of death in France, followed by cardiovascular diseases. Atrial fibrillation (AF) is one of the most common cardiac arrythmias occurring in 1% of the general population. Both cancer and AF represent common conditions but less is known about the relation between them.

An association between AF and cancer would be expected and explained by shared risk factors and epidemiology as the incidence of AF and cancer increases with age. A meta-analysis of five studies, involving 5,889,234 subjects, was published in March 2019 and studied the association of cancer and the risk of developing AF. Patients with solid cancers seemed to be at higher risk of developing AF with an OR of 1.47 (95% CI 1.31 to 1.66) and that risk was higher within 90 days of cancer diagnostic.(2)

Patients with AF are more likely to develop heart failure, stroke, or bleeding complications due to anticoagulant treatment, hence AF may affect the prognosis of malignant disease. Even though previous studies suggest that patients with cancer are at higher risk of developing AF, the association between the different types of cancer and AF remains uncertain and insufficiently described. Over the years, it has been established that people with cancer are at higher risk of venous thromboembolism but there is a lack of data concerning the risk of arterial thromboembolism. AF is one of the most important risk factors for ischemic stroke and the commonly used scores for risk stratification, such as the CHA_2DS_2-VASc score, currently does not count cancer as a variable. It is a possibility that the ischemic risk is underestimated among people with cancer. Given the increase of life expectancy, clinicians become more and more inclined to come across patients with both conditions.

We found it interesting to study the incidence of AF for different locations of cancer among the French population using the French nationwide database. In the second part, we analysed the risk of ischemic stroke in people with cancer and previous diagnosis of AF to try and determine if the coexistence of cancer and AF was at higher risk of embolic complications.

Last, we aimed to study the reliability of the two most widely used scores for risk stratification of thrombo-embolic and bleeding events associated with AF (i.e. CHA_2DS_2-VASc and HASBLED) in AF patients with cancer.

II. METHODS

Study Design

We conducted a longitudinal retrospective cohort study based on the French national hospital discharge database (PMSI Programme de Médicalisation des Systèmes d'Information) which collects information based on a coding system. Since 2004, the PMSI includes more than 67 million people from birth (or immigration) to death (or emigration). Each hospital stay and discharge from the 1546 public and private healthcare facilities in France is registered in the PMSI and the associated diagnosis are listed using the International Classification of Diseases, Tenth Revision (ICD-10). A unique and anonymous patient identification number has been developed since 2001 in order to link different hospital stays to a single patient. The reliability of PMSI data has already been assessed.

In this retrospective study, we analysed data from the PMSI database and since there was no impact on patients' care, their consent was not needed. The medical information being anonymous and protected by professional confidentiality, there was no need for ethical approval.

Similar studies have been conducted in the past and this type of study was approved by the institutional review board of the Pôle Coeur Thorax Vaisseaux from the Trousseau University Hospital (Tours, France) on December 1st, 2015, and registered as a clinical audit.

Procedures for data collection and management were approved by the Conseil National de l'Informatique et des Libertés, the independent national ethics committee protecting human rights in France, which ensures that all information is kept confidential and anonymous (authorization no. 1897139).

Study population

Patient information (demographics, comorbid conditions, medical history, and events during follow-up or hospitalization) was described using data collected in the hospital records. For each hospital stay, all diagnoses were obtained at discharge.

We collected information from patients admitted in French hospitals since 2013 and with at least 5 years of follow-up and compared the incidence of new onset AF according to the previous diagnosis of cancer. We then screened for different types of cancer based on the most common ones, according to the National Cancer Institute, and then analysed and compared the risk of developing AF for each type.

To compare the incidence of AF according to cancer type, we classified 15 types of cancer as follows: breast cancer (C50), ovarian cancer (C56, C57), uterine cancer (C53 to C55), prostate cancer (C61), renal cancer (C64, C65), bladder cancer (C67), stomach cancer (C16), colorectal cancer (C18 to C20), liver cancer (C22), pancreatic cancer (C25), lung cancer (C34), lymphoma (C81 to C85), multiple myeloma (C88, C90), leukemia (C91 to C95) and metastatic cancer (C77 to C80). The cancer ICD codes are listed in Supplemental 1.

In a second part, we included all patients over 18 years old who were hospitalized from January 2010 to December 2019 with a main or related diagnosis of AF (coded I 48 in the ICD-10) and calculated the incidence of ischemic stroke for each different types of cancer compared to patients with no cancer.

Statistical analyses

Qualitative variables were described using counts and percentages, and continuous quantitative variables as means ± standard deviation or median (interquartile range (IQR)). Comparisons were made using parametric or nonparametric tests as appropriate: the Wilcoxon W and Kruskal-Wallis tests were used for comparing values between two independent groups and the chi-square test for comparing categorical data.

For the outcomes analysis in the cohort, the incidence rates (%/year) for each outcome of interest during follow-up was estimated using hazard ratios (HRs). Univariate and multivariable analyses with Cox model were used to identify potential predictors of AF and ischemic stroke.

Receiver operating characteristic (ROC) curves were constructed, and Harrell C indexes (i.e., area under the curve) were calculated to investigate the predictive value of CHA_2DS_2-VASc and HASBLED scores in patients with and without previous cancer; the curves were compared using the DeLong test.

In all analyses, a $P<0.05$ was considered statistically significant. All analyses were performed using STATA version 16.0, Stata Corp, College Station, Texas.

III. RESULTS

a. Risk of developing AF regarding the history of cancer

In France, in 2013, we identified 3,381,472 patients hospitalized for any reason with a subsequent follow-up of at least 5 years (or dying earlier). Baseline characteristics of patients with and without cancer are presented in Table 1.

Of the 3,381,472 patients who were admitted in French hospitals in 2013, 2,968,643 (87.79%) had no history of cancer and 412,829 (12.21%) had history of cancer. People with previous cancer were older with a mean age of 68.3 ±13.1 years old compared to 58.0±22.1 for patients without cancer. There were also more men in the group with cancer than in the group without cancer (56.1 % and 45.6% respectively, p<0.0001). Patients with cancer were more inclined to have comorbidities such as hypertension (33.3% vs 19.6%, p<0,001), diabetes (16.3% vs 14.0%, p<0.001), heart failure (6.8% vs 4.8%, p<0.001), dilated cardiomyopathy, coronary artery disease (previous MI, PCI or CABG), vascular disease, ischemic stroke and intracranial bleeding, dyslipidemia, obesity, diseases related to alcohol and smoking, anemia, respiratory and chronic kidney diseases. History of atrial fibrillation was present in 9.3% of patients with history of cancer but in only 6.0 % of patients with no cancer (p<0.001).

Median of follow up was 5.4 years (interquartile range [IQR], 5.0 – 5.8 years) for patients included in the cohort.

Table 1. Baseline characteristics of patients seen in French hospitals in 2013 at least 5 years of follow-up (mean follow-up 4.7±1.8 years, median 5.4, IQR 5.0-5.8 years)

	No Previous cancer (n=2968643)	Previous cancer (n=412829)	p	Total (n=3381472)
Age, years	58.0±22.1	68.3±13.1	<0.0001	59.2±21.5
Gender (male)	1354016 (45.6)	231697 (56.1)	<0.0001	1585713 (46.9)
Hypertension	580493 (19.6)	137377 (33.3)	<0.0001	717870 (21.2)
Diabetes mellitus	415508 (14.0)	67340 (16.3)	<0.0001	482848 (14.3)
Heart failure	141573 (4.8)	27891 (6.8)	<0.0001	169464 (5.0)
History of pulmonary edema	11532 (0.4)	2747 (0.7)	<0.0001	14279 (0.4)
Valve disease	105482 (3.6)	16908 (4.1)	<0.0001	122390 (3.6)
Aortic stenosis	44547 (1.5)	6820 (1.7)	<0.0001	51367 (1.5)
Aortic regurgitation	13423 (0.5)	2773 (0.7)	<0.0001	16196 (0.5)
Mitral regurgitation	29224 (1.0)	5553 (1.3)	<0.0001	34777 (1.0)
Previous endocarditis	2334 (0.1)	651 (0.2)	<0.0001	2985 (0.1)
Dilated cardiomyopathy	47251 (1.6)	8602 (2.1)	<0.0001	55853 (1.7)
Coronary artery disease	212223 (7.1)	42292 (10.2)	<0.0001	254515 (7.5)
Previous myocardial infarction	29349 (1.0)	5095 (1.2)	<0.0001	34444 (1.0)
Previous PCI	53607 (1.8)	8277 (2.0)	<0.0001	61884 (1.8)
Previous CABG	8944 (0.3)	1524 (0.4)	<0.0001	10468 (0.3)
Vascular disease	168621 (5.7)	36126 (8.8)	<0.0001	204747 (6.1)
Atrial fibrillation	178604 (6.0)	38349 (9.3)	<0.0001	216953 (6.4)
Sinus node disease	14680 (0.5)	2624 (0.6)	<0.0001	17304 (0.5)
Previous pacemaker or ICD	66041 (2.2)	11512 (2.8)	<0.0001	77553 (2.3)
Ischemic stroke	30853 (1.0)	5067 (1.2)	<0.0001	35920 (1.1)
Intracranial bleeding	14235 (0.5)	2339 (0.6)	<0.0001	16574 (0.5)
Smoker	125370 (4.2)	32300 (7.8)	<0.0001	157670 (4.7)
Dyslipidemia	256730 (8.6)	56762 (13.7)	<0.0001	313492 (9.3)
Obesity	206682 (7.0)	35592 (8.6)	<0.0001	242274 (7.2)
Alcohol related diagnoses	111755 (3.8)	22015 (5.3)	<0.0001	133770 (4.0)
Chronic kidney disease	71660 (2.4)	14216 (3.4)	<0.0001	85876 (2.5)
Lung disease	191033 (6.4)	47674 (11.5)	<0.0001	238707 (7.1)
Sleep apnoea syndrome	83722 (2.8)	12695 (3.1)	<0.0001	96417 (2.9)
COPD	103191 (3.5)	31102 (7.5)	<0.0001	134293 (4.0)
Liver disease	62230 (2.1)	17814 (4.3)	<0.0001	80044 (2.4)
Gastroesophageal reflux	56449 (1.9)	9407 (2.3)	<0.0001	65856 (1.9)
Thyroid diseases	102045 (3.4)	21128 (5.1)	<0.0001	123173 (3.6)
Inflammatory disease	108657 (3.7)	18124 (4.4)	<0.0001	126781 (3.7)
Anemia	132130 (4.5)	66532 (16.1)	<0.0001	198662 (5.9)
Denutrition	91451 (3.1)	38690 (9.4)	<0.0001	130141 (3.8)
Cognitive impairment	62397 (2.1)	8761 (2.1)	0.39	71158 (2.1)
Illicit drug use	12687 (0.4)	984 (0.2)	<0.0001	13671 (0.4)

Values are n (%) or mean±SD. CABG=coronary artery bypass graft; COPD = chronic obstructive pulmonary disease; ICD = implantable cardioverter defibrillator; PCI=percutaneous coronary intervention; SD=standard deviation.

During follow up (mean SD, median IQ), the incidence of new onset AF was 9.63% and 9.97% in the group with no history of cancer and in the group with cancer respectively ($p < 0.001$) as seen in Figure 1. The annual incidence for patients without cancer was 2.15%/year (CI 2.14 – 2.16) compared to 3.68%/year (CI 3.68 – 3.71) for patients with cancer.

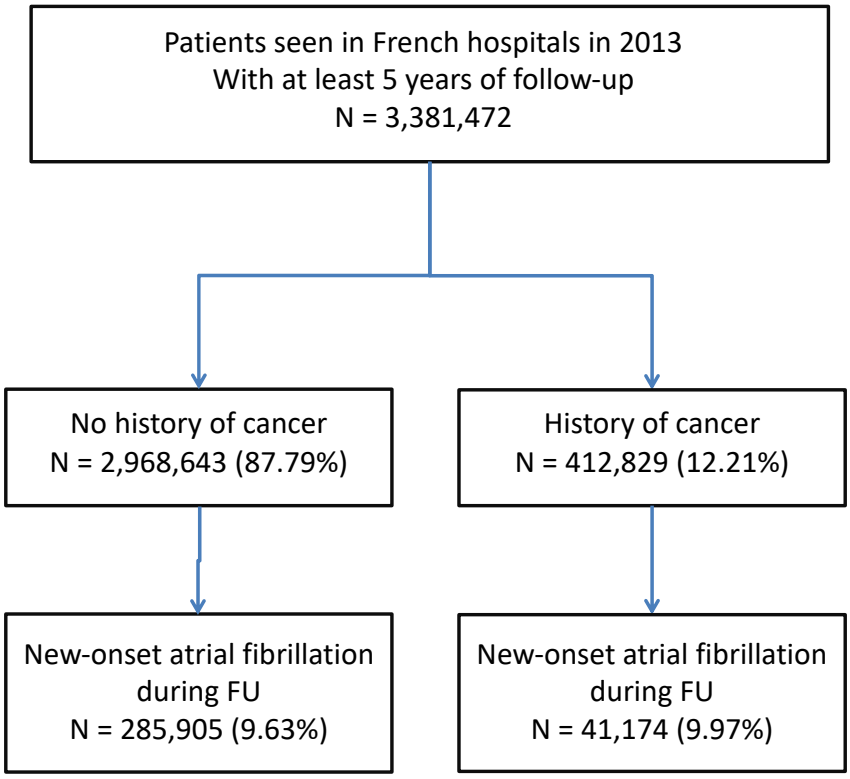

Figure 1. Flow chart of the study patients for the analysis of incident atrial fibrillation according to history of cancer.

We evaluated fourteen different types of cancer by organ in total, all presented in Table 2. Of the 412,829 patients with history of neoplastic diseases, more than half of the different cancer types were represented by the most common types: breast cancer (17.3 %), prostatic cancer (14.4%), colorectal cancer (16.7%) and lung cancer (12.3%). 144,833 patients had metastatic cancer. Lymphoma was the most common diagnosis of patients with hematologic malignancies.

Table 2. Type of cancer in patients seen in French hospitals in 2013 at least 5 years of follow-up

	Previous cancer (n=412829)
Age, years	68.3±13.1
Gender (male)	231697 (56.1)
Previous breast cancer	71359 (17.3)
Previous ovarian cancer	10956 (2.7)
Previous uterine cancer	12238 (3.0)
Previous prostatic cancer	59404 (14.4)
Previous renal cancer	15202 (3.7)
Previous bladder cancer	37684 (9.1)
Previous gastric cancer	10777 (2.6)
Previous colorectal cancer	68779 (16.7)
Previous liver cancer	14088 (3.4)
Previous pancreas cancer	13837 (3.4)
Previous lung cancer	50945 (12.3)
Previous lymphoma	22544 (5.5)
Previous leukemia	20331 (4.9)
Previous myeloma	15774 (3.8)
Previous metastatic cancer	144833 (35.1)

Values are n (%) or mean±SD.

In a univariate analysis, every cancer type showed a higher risk of developing AF except for breast and ovarian cancers which seemed at a lower risk with a HR of 0.845 (IC 0.822-0.868, p<0.0001) and 0.782 (IC 0.720-0.848, p<0.0001) respectively. Patients with lung cancer were at highest risk of developing AF with a HR of 2.210 (IC 2.145-2.276, p<0.0001).

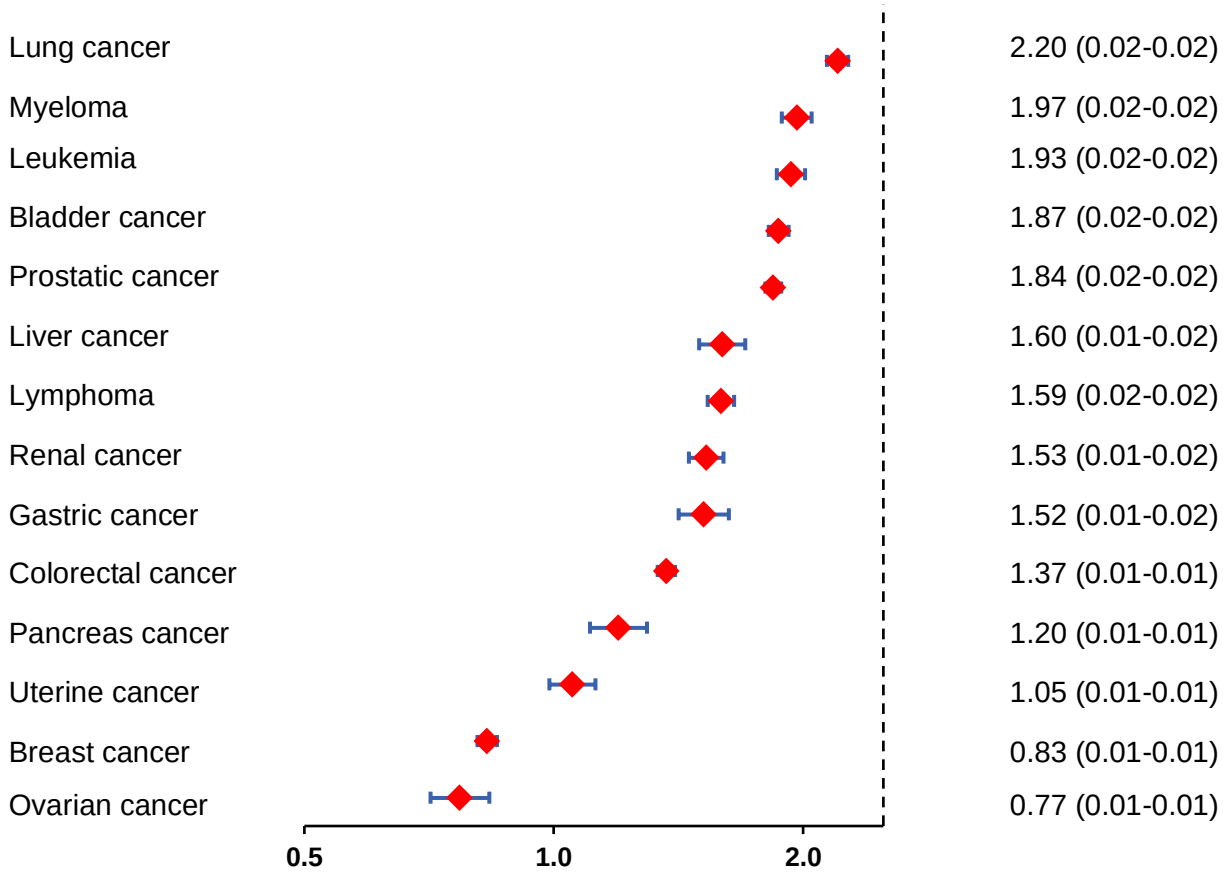

Figure 2. Risk of developing AF depending on cancer types in a univariate analysis

In a multivariable analysis, the risk of developing AF varied for every cancer type as showed in Table 3. After adjusting on the most common confounding factors such as cardiovascular risk factors, alcohol and smoking related diseases or underlying cardiomyopathy, new onset AF was more common in patients with lung cancer with a HR of 1.659 (CI 1.608 -1.711, $p<0.001$) followed by hematologic cancers. There was no statistical difference for renal, gastric, liver, uterine and pancreatic cancers. On another hand, patients with prostatic, bladder and colorectal, breast and ovarian cancers seemed less likely to develop AF.

Table 3. Predictors of AF during follow-up in patients seen in French hospitals in 2013 with at least 5 years of follow-up (mean follow-up 4.7±1.8 years, median 5.4, IQR 5.0-5.8 years).

	Univariate analysis		Multivariable analysis	
	HR, 95%CI	p	HR, 95%CI	p
Age, years	1.077 (1.076-1.077)	<0.0001	1.076 (1.075-1.076)	<0.0001
Sex (male)	1.639 (1.628-1.651)	<0.0001	1.516 (1.505-1.527)	<0.0001
Hypertension	2.848 (2.828-2.868)	<0.0001	1.118 (1.109-1.127)	<0.0001
Diabetes mellitus	1.950 (1.934-1.967)	<0.0001	1.105 (1.095-1.116)	<0.0001
Heart failure	4.582 (4.531-4.633)	<0.0001	1.579 (1.559-1.600)	<0.0001
History of pulmonary edema	2.975 (2.859-3.096)	<0.0001	1.026 (0.984-1.069)	0.23
Aortic stenosis	4.858 (4.760-4.959)	<0.0001	1.404 (1.374-1.434)	<0.0001
Aortic regurgitation	3.344 (3.238-3.454)	<0.0001	1.127 (1.089-1.166)	<0.0001
Mitral regurgitation	3.578 (3.494-3.664)	<0.0001	1.266 (1.234-1.298)	<0.0001
Previous endocarditis	2.954 (2.720-3.208)	<0.0001	1.331 (1.225-1.446)	<0.0001
Dilated cardiomyopathy	3.318 (3.258-3.380)	<0.0001	1.372 (1.346-1.400)	<0.0001
Coronary artery disease	2.803 (2.778-2.828)	<0.0001	1.208 (1.194-1.222)	<0.0001
Previous myocardial infarction	2.126 (2.079-2.173)	<0.0001	0.877 (0.855-0.900)	<0.0001
Previous PCI	2.042 (2.008-2.076)	<0.0001	0.883 (0.866-0.901)	<0.0001
Previous CABG	1.708 (1.616-1.806)	<0.0001	0.613 (0.579-0.648)	<0.0001
Vascular disease	2.519 (2.494-2.544)	<0.0001	1.088 (1.075-1.101)	<0.0001
Sinus node disease	3.904 (3.782-4.031)	<0.0001	1.214 (1.174-1.255)	<0.0001
Previous pacemaker or ICD	4.420 (4.355-4.487)	<0.0001	1.294 (1.273-1.315)	<0.0001
Ischemic stroke	2.286 (2.236-2.337)	<0.0001	1.143 (1.118-1.169)	<0.0001
Intracranial bleeding	1.373 (1.321-1.427)	<0.0001	0.889 (0.855-0.924)	<0.0001
Smoker	0.903 (0.890-0.916)	<0.0001	1.041 (1.025-1.057)	<0.0001
Dyslipidemia	1.834 (1.818-1.850)	<0.0001	0.890 (0.881-0.898)	<0.0001
Obesity	1.385 (1.371-1.399)	<0.0001	1.271 (1.257-1.286)	<0.0001
Alcohol related diagnoses	0.990 (0.974-1.005)	0.20	1.286 (1.263-1.308)	<0.0001
Chronic kidney disease	2.514 (2.477-2.551)	<0.0001	1.243 (1.224-1.262)	<0.0001
Lung disease	1.884 (1.865-1.903)	<0.0001	1.090 (1.072-1.108)	<0.0001
Sleep apnea syndrome	1.579 (1.556-1.603)	<0.0001	1.113 (1.096-1.131)	<0.0001
COPD	2.314 (2.285-2.343)	<0.0001	1.100 (1.079-1.122)	<0.0001
Liver disease	1.141 (1.119-1.163)	<0.0001	1.081 (1.058-1.104)	<0.0001
Gastroesophageal reflux	0.756 (0.740-0.772)	<0.0001	0.808 (0.791-0.825)	<0.0001
Thyroid diseases	1.316 (1.297-1.335)	<0.0001	0.982 (0.968-0.997)	0.02
Inflammatory disease	1.036 (1.021-1.052)	<0.0001	0.977 (0.962-0.992)	0.003
Anaemia	1.771 (1.750-1.791)	<0.0001	1.074 (1.061-1.087)	<0.0001
Poor nutrition	1.773 (1.742-1.805)	<0.0001	0.938 (0.921-0.956)	<0.0001
Cognitive impairment	2.367 (2.326-2.409)	<0.0001	0.823 (0.808-0.838)	<0.0001
Illicit drug use	0.290 (0.265-0.319)	<0.0001	0.939 (0.855-1.031)	0.18
Previous breast cancer	0.831 (0.809-0.854)	<0.0001	0.958 (0.932-0.986)	0.003
Previous ovarian cancer	0.770 (0.710-0.836)	<0.0001	0.903 (0.831-0.982)	0.02
Previous uterine cancer	1.053 (0.988-1.123)	0.12	1.065 (0.999-1.136)	0.06
Previous prostatic cancer	1.841 (1.801-1.882)	<0.0001	0.886 (0.867-0.906)	<0.0001
Previous renal cancer	1.528 (1.456-1.603)	<0.0001	0.953 (0.908-1.000)	0.05
Previous bladder cancer	1.869 (1.818-1.921)	<0.0001	0.914 (0.889-0.940)	<0.0001
Previous gastric cancer	1.517 (1.415-1.627)	<0.0001	0.993 (0.925-1.065)	0.84
Previous colorectal cancer	1.368 (1.335-1.401)	<0.0001	0.883 (0.861-0.905)	<0.0001
Previous liver cancer	1.597 (1.498-1.703)	<0.0001	1.036 (0.970-1.107)	0.29
Previous pancreas cancer	1.197 (1.106-1.296)	<0.0001	0.954 (0.881-1.033)	0.24
Previous lung cancer	2.201 (2.137-2.267)	<0.0001	1.659 (1.608-1.711)	<0.0001
Previous lymphoma	1.592 (1.534-1.651)	<0.0001	1.180 (1.137-1.224)	<0.0001
Previous leukemia	1.934 (1.859-2.011)	<0.0001	1.258 (1.210-1.309)	<0.0001
Previous myeloma	1.965 (1.885-2.048)	<0.0001	1.277 (1.225-1.331)	<0.0001
Previous metastatic cancer	1.234 (1.208-1.260)	<0.0001	1.190 (1.162-1.219)	<0.0001

Values are n (%) or mean±SD. CABG=coronary artery bypass graft; COPD = chronic obstructive pulmonary disease; ICD = implantable cardioverter defibrillator; PCI=percutaneous coronary intervention; SD=standard deviation.

The incidence rate of AF for each cancer type is shown in Figure 3. Patients with gynecologic cancers (including breast, ovarian, and uterine cancers) appear less likely to develop AF compared to people with no cancer over the five years of follow up.

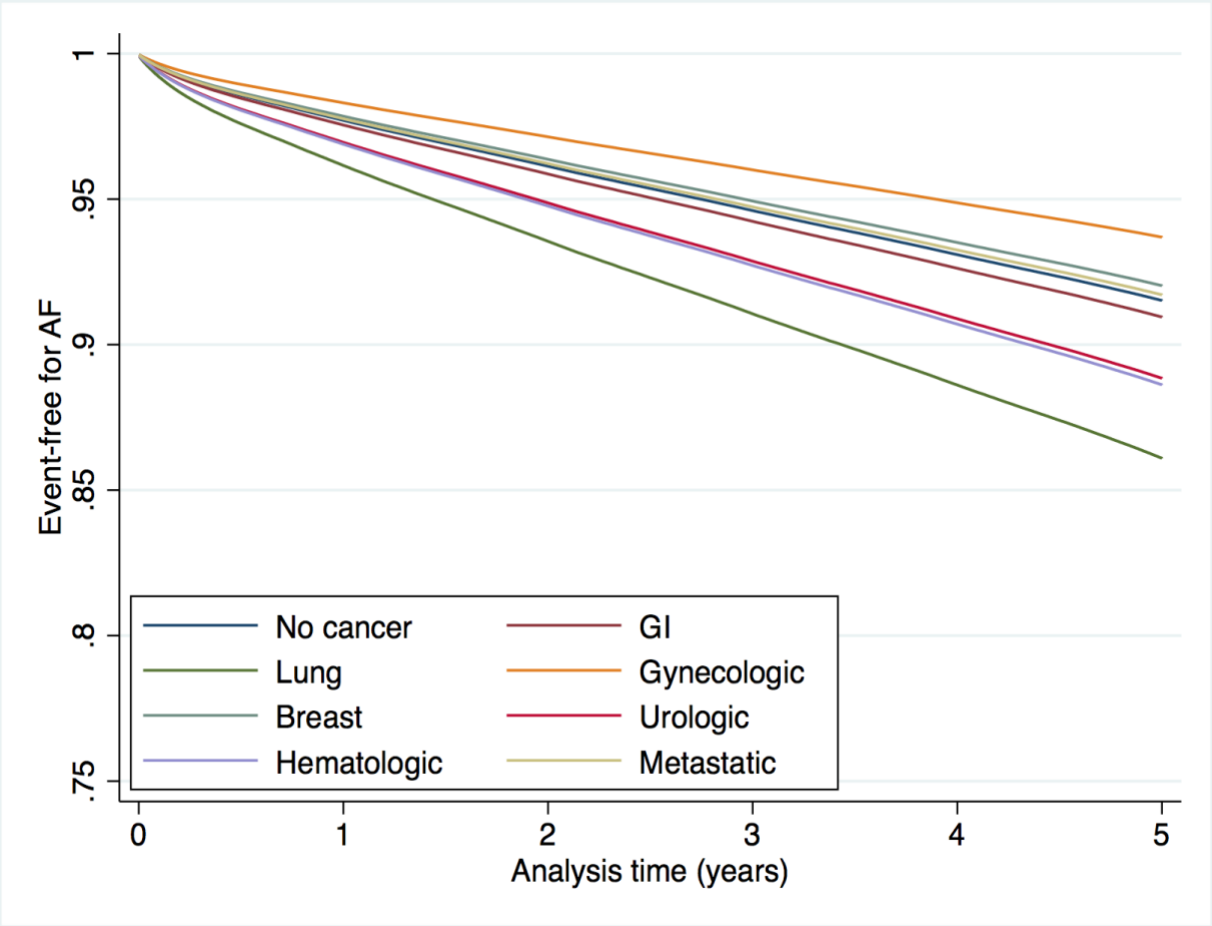

Figure 3. Event-free curves for atrial fibrillation during follow-up in patients seen in French hospitals in 2013 with at least 5 years of follow-up according to underlying cancer profile at baseline.

We conducted another analysis after adjusting only for age and sex. A history of cancer was associated with a higher risk of developing AF in most patients and the highest risk being for lung cancer with a HR of 1.912 (CI 1.856-1.969, p<0.001).

Conversely, the risk of AF was lower in patients with colorectal (HR of 0.926, CI 0.904 – 0.948, p<0.001) and prostatic cancer (HR 0.896, CI 0.876 – 0.916, p<0.001). There was no statistical difference in patients with history of breast, ovarian, gastric, and pancreatic cancers.

Table 3 bis. Predictors of atrial fibrillation during follow-up in patients seen in French hospitals in 2013 with at least 5 years of follow-up. Model adjusted for age and sex.

	HR, 95%CI	p
Previous breast cancer	0.995 (0.968-1.023)	0.74
Previous ovarian cancer	0.977 (0.900-1.061)	0.58
Previous uterine cancer	1.109 (1.040-1.183)	0.002
Previous prostatic cancer	0.896 (0.876-0.916)	<0.0001
Previous renal cancer	1.080 (1.030-1.133)	0.002
Previous bladder cancer	0.944 (0.918-0.970)	<0.0001
Previous gastric cancer	1.040 (0.970-1.115)	0.27
Previous colorectal cancer	0.926 (0.904-0.948)	<0.0001
Previous liver cancer	1.313 (1.231-1.400)	<0.0001
Previous pancreas cancer	1.023 (0.945-1.107)	0.58
Previous lung cancer	1.912 (1.856-1.969)	<0.0001
Previous lymphoma	1.230 (1.186-1.276)	<0.0001
Previous leukemia	1.307 (1.257-1.360)	<0.0001
Previous myeloma	1.342 (1.287-1.398)	<0.0001
Previous metastatic cancer	1.215 (1.190-1.241)	<0.0001

b. Risk of ischemic stroke depending on cancer type in patients with AF

In the second phase analysis, we identified 2,435,541 patients admitted or hospitalized with a main or related diagnosis of AF between January 1st, 2010, and December 31st, 2019, including 399,344 patients with a history of cancer. People with a history of cancer were mostly men (63.2 %) and slightly older (mean age of 77.9 ±10.2 compared to 77,1±12.4 years old, p<0.0001). They more frequently had cardiovascular risk factors (Table 4) and the prevalence of history of ischemic stroke was higher in patients with no previous cancer at baseline (7.4 % vs 5.7 % respectively, p<0.0001).

Table 4. Baseline characteristics of patients with AF seen in French hospitals (2010-2019)

	No Previous cancer (n=2 036 197)	Previous cancer (n=399 344)	p	Total (n=2435541)
Age, years	77.1±12.4	77.9±10.2	<0.0001	77.2±12.1
Gender (male)	1034013 (50.8)	252300 (63.2)	<0.0001	1286313 (52.8)
Hypertension	1203332 (59.1)	255733 (64.0)	<0.0001	1459065 (59.9)
Diabetes mellitus	419849 (20.6)	89768 (22.5)	<0.0001	509617 (20.9)
Heart failure	615450 (30.2)	114243 (28.6)	<0.0001	729693 (30.0)
History of pulmonary oedema	49452 (2.4)	10972 (2.7)	<0.0001	60424 (2.5)
Valve disease	287768 (14.1)	46962 (11.8)	<0.0001	334730 (13.7)
Aortic stenosis	128311 (6.3)	21481 (5.4)	<0.0001	149792 (6.2)
Aortic regurgitation	50721 (2.5)	8993 (2.3)	<0.0001	59714 (2.5)
Mitral regurgitation	123559 (6.1)	19439 (4.9)	<0.0001	142998 (5.9)
Previous endocarditis	8656 (0.4)	2081 (0.5)	<0.0001	10737 (0.4)
Dilated cardiomyopathy	145198 (7.1)	23910 (6.0)	<0.0001	169108 (6.9)
Coronary artery disease	498449 (24.5)	98260 (24.6)	0.09	596709 (24.5)
Previous myocardial infarction	101587 (5.0)	17643 (4.4)	<0.0001	119230 (4.9)
Previous PCI	80549 (4.0)	16692 (4.2)	<0.0001	97241 (4.0)
Previous CABG	9753 (0.5)	1965 (0.5)	0.27	11718 (0.5)
Vascular disease	351302 (17.3)	77224 (19.3)	<0.0001	428526 (17.6)
Sinus node disease	31758 (1.6)	3980 (1.0)	<0.0001	35738 (1.5)
Previous pacemaker or ICD	134662 (6.6)	24206 (6.1)	<0.0001	158868 (6.5)
Ischemic stroke	150970 (7.4)	22593 (5.7)	<0.0001	173563 (7.1)
Intracranial bleeding	44551 (2.2)	7948 (2.0)	<0.0001	52499 (2.2)
Smoker	121408 (6.0)	41307 (10.3)	<0.0001	162715 (6.7)
Dyslipidemia	428669 (21.1)	95820 (24.0)	<0.0001	524489 (21.5)
Obesity	286862 (14.1)	60134 (15.1)	<0.0001	346996 (14.2)
Alcohol related diagnoses	94780 (4.7)	27438 (6.9)	<0.0001	122218 (5.0)
Abnormal renal function	131586 (6.5)	35344 (8.9)	<0.0001	166930 (6.9)
Lung disease	315690 (15.5)	87569 (21.9)	<0.0001	403259 (16.6)
Sleep apnea syndrome	104348 (5.1)	22752 (5.7)	<0.0001	127100 (5.2)
COPD	172995 (8.5)	55891 (14.0)	<0.0001	228886 (9.4)
Liver disease	65477 (3.2)	23265 (5.8)	<0.0001	88742 (3.6)
Gastroesophageal reflux	42687 (2.1)	12514 (3.1)	<0.0001	55201 (2.3)
Thyroid diseases	193275 (9.5)	39955 (10.0)	<0.0001	233230 (9.6)
Inflammatory disease	114606 (5.6)	30925 (7.7)	<0.0001	145531 (6.0)
Anaemia	242097 (11.9)	113132 (28.3)	<0.0001	355229 (14.6)
Denutrition	155377 (7.6)	59919 (15.0)	<0.0001	215296 (8.8)
Cognitive impairment	203754 (10.0)	33205 (8.3)	<0.0001	236959 (9.7)
Illicit drug use	2689 (0.1)	648 (0.2)	<0.0001	3337 (0.1)
Death during follow-up	462980 (22.7)	154757 (38.8)	<0.0001	617737 (25.4)
Cardiovascular death	161765 (7.9)	25421 (6.4)	<0.0001	187186 (7.7)

Values are n (%) or mean±SD. CABG=coronary artery bypass graft; COPD = chronic obstructive pulmonary disease; ICD = implantable cardioverter defibrillator; PCI=percutaneous coronary intervention; SD=standard deviation.

We screened for the same fourteen cancer types, and they were listed in Table 5. Among the patients diagnosed with AF, 399,344 had a history of cancer with the highest prevalence for prostatic cancer (15.7%), colorectal cancer (13.7%), lung cancer (12.5%) and breast cancer (9.7%). The prevalence of cancer in patients with AF is shown in Figure 4.

Table 5. Type of cancer in AF patients seen in French hospitals (2010-2019)

	Previous cancer (n=399344)
Age, years	77.9±10.2
Gender (male)	252300 (63.2)
Previous breast cancer	38699 (9.7)
Previous ovarian cancer	4494 (1.1)
Previous uterine cancer	7670 (1.9)
Previous prostatic cancer	62710 (15.7)
Previous renal cancer	13294 (3.3)
Previous bladder cancer	32342 (8.1)
Previous gastric cancer	8470 (2.1)
Previous colorectal cancer	54755 (13.7)
Previous liver cancer	9261 (2.3)
Previous pancreas cancer	8409 (2.1)
Previous lung cancer	49737 (12.5)
Previous lymphoma	17986 (4.5)
Previous leukemia	19148 (4.8)
Previous myeloma	13081 (3.3)
Previous metastatic cancer	97606 (24.4)

Values are n (%) or mean±SD.

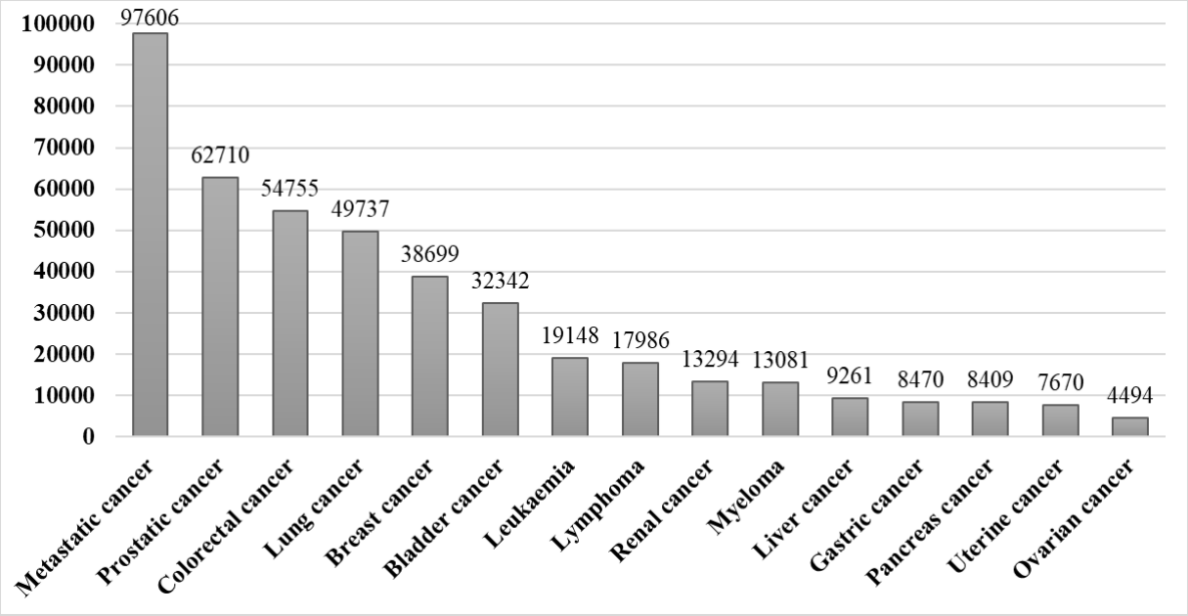

Figure 4. Prevalence of cancer types registered in atrial fibrillation patients seen in French hospitals (2010-2019).

During follow up, the number of ischemic stroke was 12,813 (IR 2.28%/year) in patients with and 98,854 (IR 2.36%/year) in patients without cancer. The risk of ischemic stroke was higher in the group with no history of cancer than in the group with cancer (4.85 % vs 3.21% respectively) as shown in Figure 5.

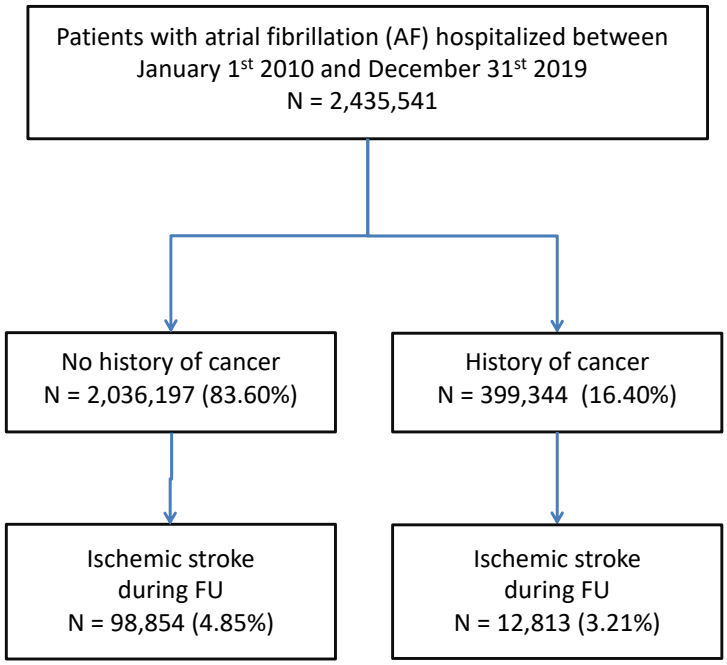

Figure 5. Flow chart of the study patients for the analysis of ischemic stroke according to history of cancer in patients with atrial fibrillation.

During the 9-year follow up, cancer was not a significant predictor of ischemic stroke (Table 6). In a univariate analysis, the only cancer type with a higher risk of ischemic stroke was breast cancer with a HR of 1.064 (95% CI 1.011 – 1.1120, P = 0.02) but no statistical difference was found after adjusting on the most common confounding factors (HR of 0.998 with 95% CI 0.947 – 1.052). On a multivariable Cox regression analysis, the presence of colorectal cancer (HR 0.884, 95%CI 0.842-0.927, p<0.0001), liver cancer (HR 0.817, 95%CI 0.700-0.954, p=0.01), leukaemia (HR 0.798, 95%CI 0.729-0.873, p<0.0001), and myeloma (HR 0.881, 95%CI 0.793-0.979, p=0.02) were inversely associated with the risk of ischemic stroke.

The risk of ischemic stroke was higher in patients with older age and comorbidities such as hypertension, diabetes, heart failure, dilated and ischemic cardiomyopathy. The history of previous ischemic stroke was associated with a 4-fold higher risk in the multivariable analysis (HR 4.611 [95%CI 4.544 – 4.679, p< 0.0001]) representing the factor with the highest weight. On the other hand, men had a lower risk of ischemic stroke with a HR of 0.864 (CI 95% 0.853 – 0.875, p< 0.0001).

Table 6. Predictors of ischemic stroke during follow-up in AF patients seen in French hospitals (2010-2019).

	Univariate analysis		Multivariable analysis	
	HR, 95%CI	p	HR, 95%CI	p
Age, years	1.038 (1.038-1.039)	<0.0001	1.033 (1.033-1.034)	<0.0001
Gender (male)	0.721 (0.713-0.730)	<0.0001	0.864 (0.853-0.875)	<0.0001
Hypertension	1.280 (1.264-1.296)	<0.0001	1.053 (1.040-1.067)	<0.0001
Diabetes mellitus	1.149 (1.133-1.165)	<0.0001	1.185 (1.168-1.202)	<0.0001
Heart failure	1.095 (1.080-1.109)	<0.0001	1.054 (1.039-1.069)	<0.0001
History of pulmonary oedema	0.987 (0.944-1.033)	0.58	1.009 (0.964-1.058)	0.69
Aortic stenosis	1.061 (1.035-1.088)	<0.0001	1.020 (0.994-1.046)	0.13
Aortic regurgitation	0.999 (0.962-1.038)	0.97	0.978 (0.940-1.018)	0.28
Mitral regurgitation	0.984 (0.959-1.010)	0.23	0.978 (0.952-1.005)	0.11
Previous endocarditis	1.388 (1.279-1.506)	<0.0001	1.428 (1.315-1.551)	<0.0001
Dilated cardiomyopathy	0.941 (0.919-0.964)	<0.0001	1.056 (1.030-1.082)	<0.0001
Coronary artery disease	1.014 (1.000-1.028)	0.05	0.997 (0.981-1.014)	0.75
Previous myocardial infarction	1.124 (1.092-1.156)	<0.0001	1.029 (0.995-1.065)	0.10
Previous PCI	0.952 (0.921-0.983)	0.003	0.975 (0.940-1.011)	0.17
Previous CABG	0.763 (0.694-0.839)	<0.0001	0.833 (0.757-0.916)	<0.0001
Vascular disease	1.250 (1.232-1.269)	<0.0001	1.168 (1.148-1.190)	<0.0001
Sinus node disease	0.832 (0.791-0.874)	<0.0001	0.846 (0.805-0.890)	<0.0001
Previous pacemaker or ICD	0.967 (0.944-0.990)	0.005	0.919 (0.897-0.941)	<0.0001
Ischemic stroke	5.198 (5.125-5.272)	<0.0001	4.611 (4.544-4.679)	<0.0001
Intracranial bleeding	2.585 (2.504-2.668)	<0.0001	1.700 (1.646-1.756)	<0.0001
Smoker	0.843 (0.821-0.865)	<0.0001	1.141 (1.109-1.174)	<0.0001
Dyslipidaemia	1.024 (1.010-1.039)	0.001	0.933 (0.919-0.947)	<0.0001
Obesity	0.765 (0.751-0.779)	<0.0001	0.877 (0.860-0.894)	<0.0001
Alcohol related diagnoses	0.955 (0.928-0.983)	0.002	1.224 (1.187-1.263)	<0.0001
Abnormal renal function	1.167 (1.138-1.196)	<0.0001	1.030 (1.004-1.057)	0.03
Lung disease	0.921 (0.905-0.937)	<0.0001	0.977 (0.953-1.000)	0.05
Sleep apnoea syndrome	0.719 (0.698-0.741)	<0.0001	0.910 (0.882-0.939)	<0.0001
COPD	0.790 (0.772-0.809)	<0.0001	0.857 (0.830-0.885)	<0.0001
Liver disease	0.892 (0.859-0.926)	<0.0001	1.004 (0.965-1.044)	0.85
Gastroesophageal reflux	0.794 (0.758-0.831)	<0.0001	0.883 (0.843-0.924)	<0.0001
Thyroid diseases	1.036 (1.015-1.057)	0.001	0.946 (0.927-0.966)	<0.0001
Inflammatory disease	1.071 (1.044-1.099)	<0.0001	0.983 (0.958-1.009)	0.21
Anaemia	1.069 (1.049-1.088)	<0.0001	0.985 (0.967-1.004)	0.13
Denutrition	1.372 (1.341-1.403)	<0.0001	1.028 (1.004-1.053)	0.02
Cognitive impairment	1.762 (1.728-1.798)	<0.0001	1.184 (1.161-1.209)	<0.0001
Illicit drug use	0.859 (0.710-1.039)	0.12	1.250 (1.033-1.513)	0.02
Previous breast cancer	1.064 (1.011-1.120)	0.02	0.998 (0.947-1.052)	0.95
Previous ovarian cancer	0.835 (0.694-1.005)	0.06	0.920 (0.762-1.110)	0.38
Previous uterine cancer	1.027 (0.909-1.162)	0.67	1.027 (0.908-1.161)	0.68
Previous prostatic cancer	0.910 (0.872-0.949)	<0.0001	0.978 (0.937-1.021)	0.31
Previous renal cancer	0.844 (0.765-0.930)	0.001	0.968 (0.878-1.067)	0.51
Previous bladder cancer	0.910 (0.858-0.965)	0.002	0.976 (0.919-1.035)	0.41
Previous gastric cancer	0.825 (0.720-0.944)	0.005	0.974 (0.850-1.116)	0.71
Previous colorectal cancer	0.839 (0.801-0.879)	<0.0001	0.884 (0.842-0.927)	<0.0001
Previous liver cancer	0.712 (0.611-0.829)	<0.0001	0.817 (0.700-0.954)	0.01
Previous pancreas cancer	0.980 (0.847-1.133)	0.78	1.105 (0.954-1.278)	0.18
Previous lung cancer	0.686 (0.641-0.733)	<0.0001	0.984 (0.918-1.055)	0.65
Previous lymphoma	0.847 (0.779-0.922)	<0.0001	0.969 (0.890-1.055)	0.47
Previous leukaemia	0.781 (0.714-0.855)	<0.0001	0.798 (0.729-0.873)	<0.0001
Previous myeloma	0.795 (0.716-0.883)	<0.0001	0.881 (0.793-0.979)	0.02
Previous metastatic cancer	0.771 (0.735-0.809)	<0.0001	0.972 (0.922-1.024)	0.28

Values are n (%) or mean±SD. CABG=coronary artery bypass graft; COPD = chronic obstructive pulmonary disease; ICD = implantable cardioverter defibrillator; PCI=percutaneous coronary intervention; SD=standard deviation.

An analysis according to cancer type showed differences in the incidence rate of ischemic stroke. Pancreatic (2.81%/year), breast (2.61%/year) and uterine cancers (2.59%/year) showed the highest IR for stroke.

Table 7. Ischemic stroke according to the presence of cancer.

	Incidence, %/year (95%CI)
	Ischemic stroke
No Cancer	2.36 (2.35-2.38)
Cancer	2.28 (2.24-2.32)
Breast cancer	2.61 (2.48-2.75) *
Ovarian cancer	2.18 (1.81-2.62)
Uterine cancer	2.59 (2.29-2.93)
Prostatic cancer	2.22 (2.13-2.32)
Renal cancer	2.08 (1.89-2.29)
Bladder cancer	2.24 (2.11-2.37)
Gastric cancer	2.16 (1.88-2.47)
Colorectal cancer	2.06 (1.96-2.15)
Liver cancer	1.94 (1.67-2.26)
Pancreas cancer	2.81 (2.43-3.25) †
Lung cancer	1.88 (1.76-2.01)
Lymphoma	2.12 (1.95-2.30)
Leukaemia	1.99 (1.82-2.18)
Myeloma	2.02 (1.82-2.24)
Metastatic cancer	2.18 (2.08-2.28)

* p=0.0002 for incidence rate ratio (1.11, 95%CI 1.05-1.16) vs no history of cancer

† p=0.02 for incidence rate ratio (1.19, 95%CI 1.02-1.37) vs no history of cancer

c. Cancer, CHA_2DS_2-VASc and HAS BLED scores

Last, we investigated the predictive values of the commonly used scores evaluating the risk of thromboembolic and bleeding events in patients with and without history of cancer.

Thromboembolism and CHA_2DS_2-VASc score

Analysis of ROC curves showed a marginally significant difference in the CHA_2DS_2-VASc score for the prediction of ischemic stroke in patients with and without cancer (Figure 6) (p=0.006 for DeLong test). This difference was not consistent in all cancer types, with a better performance of the CHA_2DS_2-VASc score in patients with breast, uterine, myeloma and metastatic cancer (Table 8).

Major Bleeding and HAS-BLED score

Predictive performance of HASBLED score was generally good with C indexes >0.70 in all cancer types (Table 8). Analysis of ROC curves for HASBLED (Figure 6) score predicting major bleeding in patients with and without cancer showed an AUC 0.821 (95%CI 0.820-0.822) in patients without cancer, and AUC 0.774 (95%CI 0.772-0.776) in patients with history of cancer (p<0.0001 for DeLong test).

Figure 6. ROC curves for CHA_2DS_2-VASc score predicting ischemic stroke (left panel) and HASBLED score predicting major bleeding (right panel) in AF patients with and without cancer.

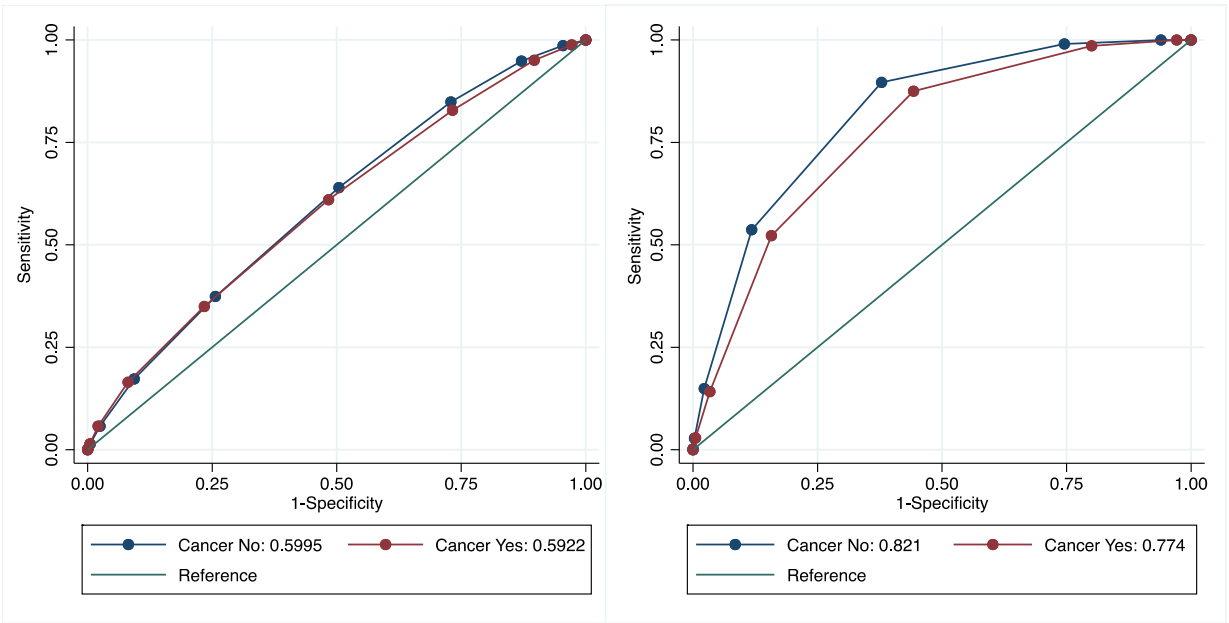

Table 8. C-statistics (95% CIs) for CHA_2DS_2VASc score predicting ischemic stroke and for HASBLED score predicting bleeding events in patients with AF and cancer, according to type of cancer.

	C-statistics (95%CI)	
	CHA_2DS_2VASc score	**HASBLED score**
Cancer	0.592 (0.587-0.597)	0.774 (0.772-0.776)
Breast cancer	0.599 (0.584-0.613)	0.810 (0.804-0.817)
Ovarian cancer	0.571 (0.518-0.624)	0.767 (0.744-0.789)
Uterine cancer	0.608 (0.573-0.642)	0.738 (0.722-0.754)
Prostatic cancer	0.587 (0.575-0.599)	0.769 (0.764-0.773)
Renal cancer	0.569 (0.541-0.598)	0.752 (0.741-0.763)
Bladder cancer	0.579 (0.562-0.596)	0.722 (0.716-0.729)
Gastric cancer	0.575 (0.536-0.614)	0.729 (0.714-0.744)
Colorectal cancer	0.583 (0.570-0.596)	0.763 (0.758-0.768)
Liver cancer	0.556 (0.510-0.602)	0.759 (0.745-0.773)
Pancreas cancer	0.574 (0.529-0.619)	0.760 (0.744-0.776)
Lung cancer	0.577 (0.558-0.596)	0.757 (0.750-0.765)
Lymphoma	0.584 (0.560-0.607)	0.761 (0.751-0.770)
Leukemia	0.588 (0.562-0.614)	0.751 (0.742-0.759)
Myeloma	0.597 (0.567-0.627)	0.771 (0.760-0.781)
Metastatic cancer	0.602 (0.589-0.616)	0.757 (0.752-0.762)

IV. DISCUSSION

Few recent studies show that for all major subtypes, a cancer diagnosis is associated with an increased risk of developing AF, but no previous study has investigated both the risk of AF in cancer patients and the risk of ischemic stroke for each cancer location in two large samples of the population.

In this population-based study, we found that: 1) patients with a history of cancer had a higher risk of AF compared to those without; 2) the risk of AF varies depending on the location of the neoplasia; 3) cancer was not a predictive factor for ischemic stroke ; 4) the CHA_2DS_2-VASc score was significantly associated with thromboembolic risk, but its predictive value was lower in AF patients with cancer compared to non-cancer patients ; 5) the HASBLED score had a good predictive performance.

Cancer and AF

In the first phase, we identified a varying risk of developing AF according to different cancer types and tumor location. In our univariate analysis, every cancer type except for breast and ovarian was associated with a higher risk of AF. Patients with lung cancer were at highest risk of AF with an HR of 2.201 (CI 2.137 – 2.267, p<0.0001) followed by hematologic cancers. These findings may be explained by the shared risk factors in patients with both AF and cancer (age, male sex, smoking and alcohol consumption, obesity). As shown in Table 1, the two groups were different with older patients and with more comorbidities in the group with previous cancer. However, the risk remained significantly higher in lung, hematological and metastatic cancers after adjusting for these factors, which suggests another underlying physiopathology.

These findings expand previous evidence from a Danish population-based study that showed varying risks of AF according to cancer type. Lung cancer showed the highest risk of AF, with an HR of 3.16 (95% CI 3.04 - 3.30).(3) The strong correlation between lung cancer and AF suggests a direct impact due to the close relationship between the two organs. The anatomical location of the tumor may be an important factor for development of AF.

More specifically, patients diagnosed with breast or ovarian cancer were younger and with less comorbidities, thus less inclined to have AF. Gastric and pancreatic cancers were not associated with a higher risk of AF which may be explained by the poor prognosis hence a shorter follow up period. Patients with prostatic and colorectal cancers had a statistically significant lower risk of developing AF in our study. One possible hypothesis is that prostatic and colorectal cancers both benefit from mass screening and could be diagnosed at an earlier stage with smaller tumours and thus leading to less aggressive therapies.

Many pathophysiological hypotheses have been presented, all in favor of a multifactorial mechanism. First, neoplastic diseases provide the basis for a chronic inflammatory state and this systemic inflammation could contribute to atrial remodelling that could promote AF. Moreover, the autonomous dysregulation due to pain, physical or emotional stress may increase sympathetic system, altering the balance between sympathetic and parasympathetic nervous system which could induce changers of atrial electrophysiology.(4,5) Other potential drivers include cancer related comorbidities with metabolic and electrolyte disorders, infections, hypoxia, anemia, and malnourishment which could also contribute to AF. In addition, we have to take into account the role of medical therapy for cancer with surgery (oncological pulmonary

surgeries being the most described in recent literature)(6), thoracic radiation and anti-cancer drugs. (7,8) Sporadically, arrhythmic complications can be caused by direct tumors effect with cardiac tumors or metastases compressing the atria.

Our results are therefore biologically plausible and add significant clinical data to the knowledge, but more studies are needed to fully understand the relationship between cancer and new-onset AF.

Cancer and ischemic stroke

In a second phase, our study showed that cancer was not a significant predictor for ischemic stroke.

The risk of ischemic stroke was higher in patients with older age and comorbidities such as hypertension, diabetes, heart failure, dilated and ischemic cardiomyopathy and the history of previous ischemic stroke. Men had a lower risk of ischemic stroke. All these factors constitute the well-known items in the validated CHA_2DS_2-VASc score. These findings are consistent with recent literature as a Danish nationwide analysis including 11,855 patients with and 56,264 without cancer showed no association between cancer and stroke.(9)

Physio pathological studies suggest that the platelet activation and prothrombotic state in cancer would be associated with a higher risk of arterial embolic complications.(10,11)

One hypothesis that could explain the opposite findings in our study is that people with cancer have a closer medical follow up allowing an earlier diagnosis of arrythmia, hence a better prevention of embolic complications with an adequate blood thinner prescription.

Colorectal cancer, liver cancer, leukemia and myeloma were inversely associated with ischemic stroke, but these inverse associations do not indicate patients at lower risk of stroke. These patients are indeed more likely to suffer from other types of complications, such as bleeding or all-cause and cardiovascular mortality, which we didn't evaluate in our study. These complications and the competing risk of mortality should be taken into consideration in the interpretation of the results to avoid an underestimation of thromboembolic risk.

Cancer and scores

The CHA_2DS_2-VASc score was significantly associated with thromboembolic risk, but its predictive value was modest and statistically lower in patients with AF and cancer compared to non-cancer patients. This finding is consistent with a previous study including 122,053 patients with AF, of whom 12,014 (10%) had recent cancer and showed that the CHA_2DS_2-VASc score was associated with a dissimilar increase in the risk of thromboembolism for patients with and without cancer. (12) The CHA_2DS_2-VASc score is reliable in patients with AF cancer but should be used and interpreted with caution. More studies are needed to validate the use of the CHA_2DS_2-VASc score among patients with cancer.

The predictive performance of HASBLED score was good with C indexes >0.70 in all cancer types. One hypothesis to explain the good predictive value of the HAS BLED score is that the data is easily collected as patients with cancer are more likely to have experienced previous bleeding events or suffer from predisposition defined by anemia.

The management of this unique group of patients must require an interdisciplinary approach including cardiologists, oncologists, and other subspecialists. Physicians should take into consideration the type of cancer, its prognosis, and the bleeding risk to better evaluate the clinical risk for ischemic or bleeding complications.

Strengths and limitations

The strength of this study is related to its real-world observational design with a very large sample of the French population and to the reliability of the PMSI data that has already been assessed in previous studies. Our study however has several limitations. As we conducted a retrospective cohort study, the missing information may be an important confounding factor.

First, we included patients with a history of cancer but had no information concerning the delay between the two diagnoses of cancer and AF. The results may vary depending on whether the focus was on patients with active cancer or in remission. Also, we lack information concerning the stages of cancer to fully understand the relation between cancer and AF. Indeed, metastatic cancers were at

higher risk of AF (HR 1.190, CI 1.162-1.219, p<0.001) but we did not identify neither the original location of the neoplastic disease nor the location of the metastasis.

Second, no information on treatment - either medical, surgical or radiation - was available and this may have impacted our results given that treatment strategies can affect the risk of AF.(6–8) Furthermore, lack of data on the quality of oral anticoagulation may be an important confounding factor in the evaluation of the risk of ischemic stroke.

Additionally, our study did not include patients with AF diagnosed outside of French hospitals and solely treated by general practitioners or cardiologists. This could potentially lead to an underestimation of the incidence of AF in both groups. Misclassification of the diagnosis based on the ICD code is also possible, but any misclassification can be considered small and the use of the French database has already been used and validated in previous studies.

Last, we did not analyse in our study the possible influence of competing risk between cardiovascular and non-cardiovascular events in AF patients with cancer or no cancer.

V. CONCLUSION

Our nationwide study showed that patients with a history of cancer had a varying risk of AF depending on tumor location; patients with lung or hematological cancer had a higher risk whereas patients with prostatic, bladder and colorectal, breast and ovarian cancers seemed less likely to develop AF.

The risk of ischemic stroke was lower in patients with cancer but it is important to take into account the competing risk of other complications that were not recorded in our study.

Both the CHA_2DS_2-VASc and the HAS-BLED scores can be used to evaluate the ischemic and bleeding risk in cancer patients but should be interpreted with caution as we lack hindsight in this particular population.

Our study rises awareness of the risk of AF in cancer patients and clinicians should consider the type and location of cancer to provide individualized care.
Further studies are needed to evaluate the impact of AF on the outcomes of patients with cancer.

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VII. APPENDIX

Gynaecologic	Breast Ovarian Uterine	C50 C56, C57 C53, C54, C55
Urologic	Prostate Kidney Bladder	C61 C64, C65 C67
Digestive	Stomach Colorectal Liver Pancreatic	C16 C18, C19, C20 C22 C25
Pulmonary	Lung	C34
Hematologic	Lymphoma Leukaemia Myeloma	C81, C82, C83, C85 C91, C92, C93, C94, C95 C88, C90
Metastatic		C77, C78, C79, C80

Supplemental 1 – Cancer ICD codes

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MARANG Amélie 39 pages – 9 tableaux – 6 figures

Résumé :

Introduction. Un lien entre cancer et incidence de FA est envisagé depuis quelques années et la FA affecte le pronostic des patients. Notre objectif est d'étudier le risque de développer de la FA ainsi que le risque d'AVC ischémique selon les différentes localisations de la maladie néoplasique et d'évaluer l'applicabilité des scores de risque.

Méthodes. Cette étude de cohorte française porte sur la base de données nationale du PMSI : 3 381 472 patients hospitalisés en France en 2013 ont été inclus et nous avons comparé l'incidence de FA puis étudié l'incidence d'AVC ischémique au sein d'une deuxième population de FA (2010-2019) selon les différents cancers.

Résultats. Parmi les 3 381 472 patients, 421 829 avaient un antécédent de cancer et les patients avec un antécédent de cancer avaient un risque plus élevé de développer de la FA (9.97% vs 9.63%, p<0,001). Le risque était le plus élevé chez les patients avec un cancer du poumon (HR à 1,673, p<0,001), suivi par les cancers hématologiques, de l'utérus et du foie. Il n'y avait pas de différence significative chez les patients atteints de cancer du rein, de l'estomac et du pancréas. Les patients avec un cancer de la prostate, de la vessie, colorectal, du sein ou des ovaires semblaient, eux, moins à risque de développer de la FA. Au sein des 2 435 541 patients avec de la FA, le risque d'AVC ischémique était plus bas chez les patients avec un antécédent de cancer. Les scores HAS BLED et CHA_2DS_2-VASc semblent pertinents pour évaluer les risques ischémique et hémorragique.

Conclusion. Les patients aux antécédents de cancer, en particulier du poumon, semblent plus à risque de développer de la FA et le risque varie selon la localisation du cancer. Il ne semble pas y avoir de sur risque d'AVC ischémique chez les patients aux antécédents de cancer. Les scores de risque sont applicables mais sont à interpréter avec précaution par le clinicien.

Mots clés : Fibrillation atriale, cancer, AVC ischémique, onco-cardiologie

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