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## Atrial fibrillation in cancer patients: Hindsight, insight and foresight

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## ABSTRACT

An increase of atrial fibrillation (AF) incidence in cancer patients has recently been pointed out, with complex interrelationships between these two entities on top of surgery factors.

Most of present knowledge comes from retrospective studies or data from registries but the underlying mechanisms of the association between atrial fibrillation and cancer are still unclear. An increased risk of AF in cancer patients could represent a major public health problem although scarce information is available for the challenging management of such patients with distinctive features, especially in terms of antithrombotic therapy. Elaborate evidence-based approaches are thus required. This review provides an insight into AF among cancer patients through an overview of the underlying mechanisms, epidemiology evidence and future therapeutic challenges.

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## 1. Introduction

Atrial fibrillation (AF) concerns more than 33 million people, with an increasing incidence, and is associated to morbidity and mortality such as, for instance, systemic embolic complications (including ischemic stroke), heart failure, cognitive dysfunction and death. Beside AF of patients with cardiovascular diseases, AF can occur in a wide variety of conditions such as thyroid disorder, obstructive sleep apnea, chronic obstructive pulmonary disease and sepsis [1]. Recent data pointed out an increase of AF incidence among cancer patients, raising substantial concerns, notably regarding prognosis and treatment of cancer as AF may represent a major hindrance to cancer management [2]. An increased risk of AF in cancer patients could represent a major public health problem as cancer will affect one in two people by 2020 partly due to an aging population (which is also a major risk factor for both AF and AF-related complications as stroke). The improvements in cancer therapy have led to an increase in survival, but also in oncologists' concerns about medium and long-term complications [3,4]. It seems that inflammatory conditions, which are critical components of the neoplastic process may promote AF and be the common denominator for both entities, along with the autonomic nervous system impairment [5,6]. Thereby, more in-depth knowledge

about pathogenesis and epidemiologic links between AF and cancer are required in order to improve therapeutic management of cancer patients with new onset AF, which remains another major issue. As a matter of fact, there are currently no available clinical guidelines in the management of AF following cancer diagnosis, notably in terms of antithrombotic treatment choice [4]. If AF remains a common reason for chronic warfarin use, it seems that cancer patients, who receive warfarin for deep venous thrombosis (DVT) and/or pulmonary embolism (PE), have worse anticoagulation control and worse outcomes in comparison with cancer-free patients [7]. Besides, the role and safety of direct oral anticoagulants (DOACS) in patients with cancer remains to be clarified as well as the CHA<sub>2</sub>DS<sub>2</sub>-VASc and HAS-BLED scores which have not been validated in this category of patients [4]. Clinical relevant data on treatment, duration, risk of embolic events and particularly ischemic strokes in cancer patients with AF are scarce in the literature. This review provides an insight into AF among cancer patients, and its substantial characteristics through an overview of underlying mechanisms, epidemiological evidence and future therapeutic challenges.

## 2. AF in cancer patients: intricacies and epidemiological grounds

The epidemiological evidence for an association between AF and cancer is relatively recent and mainly relies on scarce data. Early research studies on this subject, dating from the mid-nineties, primarily mentioned an increased risk of AF after oncologic thoracic surgery,

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making postoperative AF, a highly explored entity now well-known [8, 9]. Indeed, beyond thoracic surgery, the occurrence of AF after surgery has been afterwards reported for colorectal cancer or esophageal cancer with substantial prevalence ranging respectively between 4% and 10% [10,11]. On the strength of these findings, additional studies confirmed that AF had a negative impact on prognosis, especially after pulmonary resection for lung cancer, with higher rates of morbi-mortality [12]. However, if the initial link between AF and cancer was mostly based on cancer surgery and its consequences, it has gradually become clearer that patients with cancer at the time of diagnosis, prior to any treatment, were at higher risk to develop AF and that AF could also occur postoperatively. Close links between AF and cancer outside the postoperative period have been reported by several case-control studies and support the argument that cancer in itself may be a comorbid state predisposing to AF. In a case-control study investigating the risk of colon cancer among 12,304 veterans taking nonsteroidal anti-inflammatory drugs, Muller et al. were the first to note a positive association between AF and cancer, as AF was more commonly found in veterans with colon cancer (odds ratio, 1.34 [95% CI, 1.16–1.55]) [13]. Other case control studies among non-surgical populations have led to similar findings in different types of cancers, such as colorectal, kidney, breast or ovary cancers and also focused on persons with recent cancer diagnoses or patients who were admitted to hospital for cancer treatment, suggesting that cancer itself is a comorbid condition that predisposes to AF instead of a postoperative complication [14–17]. Indeed, as associations between surgery or chemotherapy and AF were avoided, thus suppressing possible confounding factors, a sharper distinction must be drawn between two main situations: a pre-existing AF before cancer diagnosis and a new-onset AF occurring after the diagnosis of cancer with possibly respective etiopathogenesis. Epidemiological data of AF in cancer patients are summarized in Table 1.

### 3. Interconnections between AF and cancer: towards a new paradigm?

Over the past three years, large cohort studies, working from these epidemiological retrospective premises, significantly enhanced the

mentioned findings. So far, it appears that cancer increases the risk of AF, but leaves unexplained the hypothesis that AF could be a marker of occult cancer and thus if cancer screening in patients with new-onset AF should be considered. To this end, a cohort study of 269,742 patients based on Danish registry data, highlighted that patients who were diagnosed with AF had a 5 times increased risk of cancer diagnosis in the first 3 months of their AF diagnosis, which represents a 2.5% absolute risk of cancer diagnosis (95% CI, 2.4%–2.5%). The relative risk of cancer diagnosis was clearly high for all types of cancer within 3 months after AF diagnosis, but was even more pronounced for lung, kidney and colon cancers. Consequently, the authors underline the potential role of AF as a marker for occult cancer, and question the interest of an extensive cancer screening at AF diagnosis in selected patients, as a way to improve prognosis [18].

The interconnection of both entities has also been investigated by Conen et al., in a long-term prospective cohort study of 34,691 women aged 45 or older. Women were followed up between 1993 and 2013 for incident AF and malignant cancer within the Women's Health Study, a randomized clinical trial of aspirin and vitamin E for preventing cardiovascular diseases and cancer. The findings published in 2016 showed that women with new-onset AF had a significantly increased risk of incident cancer during subsequent follow-up, even after extensive adjustment for age (hazard ratio, 1.58 [95% CI, 1.34–1.87]) and other potential cofounders including cardiovascular diseases, diabetes, smoking, and alcohol consumption (hazard ratio, 1.48 [95% CI, 1.25–1.75]). The risk of cancer was 3-fold higher within 3 months of AF diagnosis (hazard ratio, 3.54 [95% CI, 2.05–6.1]) and remained significant beyond 1 year (hazard ratio, 1.42 [95% CI, 1.18–1.71]). Of the examined cancer subtypes, AF was most strongly associated with colon cancer, probably due to the use of anticoagulants among patients with AF and occult colon cancer that may have led to bleeding and then, earlier detection. In contrast, the risk of incident AF after cancer diagnosis was 20% higher in the first 3 months, but not beyond. The authors also highlight that cancer and AF do share risk factors which might underlie their interrelation and subsequently, this study could not exclude that possibility. A number of coexisting comorbidities including smoking, obesity and alcoholism as well as aging are known to predispose both

**Table 1**  
Epidemiological evidence of AF in cancer patients.

Type of study, year	First author	Type of cancer	Number of patients	HR	OR	SIRs	AF prevalence	95% CI	References
Prospective single-center study 2005	Roselli et al.	Lung cancer resection	604	UK	UK	UK	19%	UK	[9]
Prospective single-center study 2012	Imperatori et al.	Lung cancer resection	454	UK	UK	UK	9.9%	UK	[12]
Retrospective study 2005	Siu et al.	Elective surgery for colorectal cancer	563	UK	UK	UK	4.4%	UK	[10]
Prospective single-center study 2013	Ojima et al.	Esophageal cancer resection	207	UK	UK	UK	9.2%	UK	[11]
Case-control study 1994	Muller AD et al.	Colon cancer	12,304	1.34	UK	UK	UK	1.16–1.55	[13]
Case-control study 2002	Guzzetti et al.	Colorectal cancer	456	UK	3.5	UK	5.2%	1.6–7.2	[14]
Prospective single-center study 2008	Guzzetti et al.	Colorectal or breast cancer	1317	UK	3.3	UK	3.6%	1.67–6.61	[15]
Case-control study 2012	Erichsen et al.	Colorectal cancer	28,333	UK	7	UK	0.59%	6.3–7.8	[16]
Cohort study 2012	Hu et al.	All cancers combined	24,125	UK	UK	UK	2.4% at cancer diagnosis/1.8% after cancer diagnosis	UK	[17]
Cohort study 2014	Ostenfeld et al.	All cancers combined	269,742 with new-onset AF	UK	UK	5.11	UK	4.99–5.24	[18]
Cohort study 2016	Conen et al.	All cancers combined	34,961	1.58	UK	UK	4.2%	1.34–1.87	[2]

SIRs: standardized incidence ratios.

HR: hazard ratio.

OR: odds ratio.

UK: unknown data.

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