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EDITORIAL COMMENT

Atrial Fibrillation and Cancer

Where Biology and Epidemiology Intertwine*

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Patients with cancer have an increased risk for atrial fibrillation (AF), with a recent meta-analysis of observational studies demonstrating an approximately 47% higher risk of AF in patients with cancer compared with patients without cancer (1). The two conditions share common pathophysiological mechanisms and risk factors (2), and some cancer treatments predispose to AF. Perhaps owing to common risk factors, the relationship between cancer and AF appears to be bidirectional: An increased risk of incident cancer in patients with known AF has also been demonstrated (3).

Importantly, the range of AF risk across different types of cancer has been incompletely characterized previously. The study by Yun et al. (4) in this issue of *JACC: CardioOncology* provides important insights regarding the relationship between cancer and AF and adds to our understanding of AF risk in distinct cancer types. The authors should be commended for their thoughtfully conducted investigation that advances the field and potentially informs our care of patients.

Yun et al. (4) report on a nationwide Korean population-based analysis of administrative insurance claims in more than 800,000 patients with 19 different cancer types (including solid and hematologic malignancies) who were matched 1:2 by age and sex to control subjects without cancer. During a median follow-up period of 4.5 years, 3.1% of patients with cancer developed AF, a larger proportion than the 1.9% of control subjects. The median times from cancer diagnosis to incident AF were 1.7 and 3.2 years in the cancer and control cohorts, respectively. Patients with cancer were found to have a 1.6-fold higher AF risk than the general population even after adjusting for well-established AF risk factors such as hypertension, diabetes, dyslipidemia, obesity, chronic kidney disease, smoking, alcohol consumption, physical exercise status, and income level. Importantly, the risk of AF varied substantially across the 19 cancer types. Multiple myeloma was most strongly associated with AF (adjusted hazard ratio [HR]: 3.34), followed by esophageal cancer (adjusted HR: 2.69). Thyroid and stomach cancer were most weakly associated with AF (HR: 1.32 and 1.27, respectively).

The results of this analysis are largely consistent with evidence from a nationwide analysis from Denmark despite differences in study design and populations (5). In that analysis of 300,000 cancer patients, lung, upper digestive, and hematologic cancers demonstrated the strongest risks for incident AF. The fact that the risk of AF varies across different types of cancers does not surprise us. Cancer is heterogeneous in terms of epidemiology, pathogenesis, systemic effects, and treatment modalities, such that we would not expect a uniform risk of AF across cancers. The shared risk factors for AF and cancer are stronger for certain cancers, although age is one of the most powerful risk factors for most cancers in addition to being a powerful risk factor for AF. Obesity, smoking, and alcohol are risk factors for AF that are strongly linked to esophageal cancer but not to thyroid cancer (6). Although the study by Yun et al. (4) controlled for hypertension, diabetes, dyslipidemia, obesity, kidney disease, smoking, alcohol, exercise, and income, it is possible that difficulties with accurate data collection for some of these factors impaired adjustments and may have partly

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contributed to the associations between AF and certain cancers. In addition, common pathophysiologic pathways (e.g., inflammation) (7,8) and the use of arrhythmogenic medications to treat specific cancers may have played roles as well. The contribution of risk factors versus underlying biological mechanisms versus oncologic treatment toxicity to AF pathogenesis may vary by cancer type. For example, for multiple myeloma, medications are probably responsible for the bulk of the increased AF risk, but systemic inflammation also may be relevant (9). In contrast, the increased risk of AF in patients with esophageal cancer may be primarily due to smoking and alcohol, which might be underreported or underascertained in large administrative datasets.

The timing of AF after cancer is of interest. In the analysis by Yun et al. (4), the cancer-associated risk of AF was highest in the first 90 days after the cancer diagnosis. This may reflect increased opportunities for incidental diagnoses of previously unrecognized AF during the frequent health care encounters that occur soon after a new cancer diagnosis (detection bias). Alternatively, this observation could be explained by the hypothesis that surgical, medical, and radiation treatments administered soon after a cancer diagnosis are directly linked to a considerable portion of the cancer-attributable risk of AF. Postoperative AF after noncardiac surgery, including oncologic surgery, is common (10). Among solid tumors, intrathoracic malignancies (esophageal and lung) demonstrated some of the strongest associations with AF in both the current study (4) and the Danish study (5), perhaps owing in part to the increased risk of AF after thoracic surgery as a result of direct myopericardial irritation. Cancer surgeries can also lead to autonomic dysregulation, increased physical and emotional stress, and fluid and electrolyte imbalance, all of which can trigger AF. Regarding the contribution of systemic therapies, various antineoplastic agents, including anthracyclines, alkylating agents, human epidermal growth factor receptor-2/neu-targeting therapies, and immunotherapies have been associated with cardiotoxicity, which may predispose to AF (11). Most notably, ibrutinib, a tyrosine kinase inhibitor that is used to treat chronic lymphocytic leukemia and other hematologic malignancies, can lead to a 10-fold risk of incident AF due to the off-target inhibition of the C-terminal Src kinase causing deleterious downstream proarrhythmic effects (12). In a pooled analysis of ibrutinib trials, the median time to onset of AF was 2.8 months (range: 0.3 to 17.5 months) after initiation (13).

How can the results of the study by Yun et al. (4) inform our practice? The authors' proposal for increased vigilance for AF detection in the cancer types associated with the highest risks of AF is intriguing, but we do not yet know if we can identify a subset of patients with cancer who will meaningfully benefit from AF screening. In the general population of asymptomatic older adults, the value and optimal methods for AF screening remain controversial (14), and there are more uncertainties in patients with cancer. A key limitation of the study by Yun et al. (4) is that it does not address AF treatments and how they affect outcomes in cancer patients. While rhythm control and anticoagulation interventions can prevent complications such as stroke and heart failure, the implementation and outcomes of these treatments are more complex in patients with both cancer and AF owing to competing factors such as interacting medications and excess bleeding risks, and because cancer may limit life expectancy in many cases (15).

Advances in deep-learning artificial intelligence applied in large digitized clinical datasets have enabled the development of algorithms for the detection of silent concomitant or imminent AF from the routine 12-lead electrocardiogram in sinus rhythm (16), but the potential value of this approach is only beginning to be evaluated. Such a screening approach could be applied to populations at risk, including patients with certain cancers, to enable the timely detection of the arrhythmia and institution of treatments to prevent long-term complications.

The coexistence of cancer and AF will be an increasing problem owing to the aging population and improved survival of cancer patients thanks to ever-improving antineoplastic strategies. This and other studies highlight the complex link between cancer and AF. The need to fill the gaps in evidence surrounding AF pathogenesis and optimal screening and management is becoming increasingly pressing.

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