The Correlation with New-Onset Atrial Fibrillation and Increased Cancer Risk

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Abstract

Background: Atrial fibrillation (AF) is one of the most common heart arrhythmias world-wide with Americans >40 years old having a lifetime risk of 26% for men and 23% for women. It is estimated that 2.3 million adults in the United States are currently diagnosed with AF with an expected increase to 5.6 million by the year 2050. AF is strongly associated with significant cardiovascular (CV) and cerebrovascular complications such as heart failure, stroke and myocardial infarction, as well as non-CV causes of death including cancer. Previous investigative focus has been on incidence of AF post-cancer diagnosis or as sequela following cancer treatment. This systematic review is aimed at assessing the incidence of AF prior to cancer diagnosis and potential utilization in preventative cancer screening.

Methods: An exhaustive search of current literature was performed using MEDLINE-Ovid, CINAHL and Web of Science. Keywords used included: atrial fibrillation, neoplasms and risk. Bibliographies of resulting articles were referenced for additional relevant studies. Articles selected for review were published in the English language, were exclusive to human subjects and investigated AF preceding cancer diagnosis. Articles were assessed for quality using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE).

Results: The literature search yielded a total of 202 studies; two observational cohort studies met the designated criteria for this systematic review. Both observational studies demonstrated a correlation between new onset AF and subsequent cancer diagnosis.

Conclusion: Two observational studies revealed a correlation between new onset AF and cancer diagnosis, specifically colorectal and lung cancers. The quality of evidence is moderate given the high likelihood of detection bias; additionally these studies could not be directly compared due to the different populations included in the research. There is also the question of what to do with this information as cancer screening often involves expensive and invasive procedures. Given that AF is one of the most common arrhythmias worldwide, it would be unreasonable to subject such a vast number of individuals to these unnecessary screenings. However, it is reasonable to expect future studies to investigate this correlation in a large diverse population in effort to assess a more accurate level of cancer risk in those who are newly diagnosed with AF.

Keywords: Atrial fibrillation, cancer, neoplasms, and risk

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The Correlation with New-Onset Atrial Fibrillation and Increased Cancer Risk

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Clinical Graduate Project Coordinator: Annjanette Sommers, PA-C, MS
BIOGRAPHY

Jessica Sclafani is originally from Connecticut where she received her undergraduate degree in kinesiology from Sacred Heart University. Following completion of her undergraduate degree, she began working as a health and wellness consultant for GE corporate. Subsequently, her strong interest in cardiology led her to work as a certified clinical research coordinator for Cardiology Associates of Fairfield County in Connecticut. She is currently attending the physician assistant program at Pacific University with the ambition to pursue a career in pediatric cardiology following graduation.
ABSTRACT

Background: Atrial fibrillation (AF) is one of the most common heart arrhythmias world-wide with Americans >40 years old having a lifetime risk of 26% for men and 23% for women. It is estimated that 2.3 million adults in the United States are currently diagnosed with AF with an expected increase to 5.6 million by the year 2050. AF is strongly associated with significant cardiovascular (CV) and cerebrovascular complications such as heart failure, stroke and myocardial infarction, as well as non-CV causes of death including cancer. Previous investigative focus has been on incidence of AF post-cancer diagnosis or as sequel following cancer treatment. This systematic review is aimed at assessing the incidence of AF prior to cancer diagnosis and potential utilization in preventative cancer screening.

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Keywords: Atrial fibrillation, cancer, neoplasms, and risk
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Thank you to the Pacific University faculty for making this journey much less arduous than I had anticipated.
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Table I: Quality Assessment of Reviewed Studies

Figure I: Prevalence of AF in Sub-Groups of Cancer vs. Non-Cancer Patients

LIST OF ABBREVIATIONS

AF                Atrial fibrillation
CV                Cardiovascular
HR                Hazard Ratio
SIR               Statistical Information on Recidivism
The Correlation with New-Onset Atrial Fibrillation and Increased Cancer Risk

BACKGROUND

Atrial fibrillation (AF) is one of the most common heart arrhythmias world-wide with Americans >40 years old having a lifetime risk of 26% for men and 23% for women\(^1\) confirmed by a European population study\(^2\) with lifetime risk of 23.8% for men and 22.3% for women. It is estimated that 2.3 million adults in the United States are currently diagnosed with AF with an expected increase to 5.6 million by the year 2050.\(^3\)-\(^4\) Approximately 75% of patients diagnosed with AF will have a life threatening hospitalization or expire due to complications within 20 years of their diagnosis, which is a 3-fold increase compared to those without an AF diagnosis.\(^5\) AF is strongly associated with significant cardiovascular (CV) and cerebrovascular complications such as, heart failure, stroke and myocardial infarction. AF is also associated with non-CV causes of death, most specifically: cancer.\(^6\)

While heart disease remains the leading cause of death in the United States, cancer follows closely behind as the second most prevalent cause of death.\(^6\) The World Health Organization reported that in the year 2012, 14.1 million people were newly diagnosed with cancer and of those diagnosed, 8.2 million resulted in death.\(^7\) The CDC estimates that by the year 2025, 19.3 million new cancer cases per year are expected to be diagnosed.\(^8\) The leading cancer deaths across all genders and races in the United States include: lung, breast and colorectal cancer.\(^8\)

Current focus has been placed on the early detection and prevention of cancer due to worldwide disease prevalence, as well as, the emphasis on preventative medicine.\(^8\)
in recent years. Previous studies\textsuperscript{9,10} have investigated the incidence of AF post-cancer diagnosis, or as sequela post-cancer treatment. A correlation between cancer diagnosis and/or treatment and new AF diagnosis has been established. Specifically looking at lung cancer requiring thoracic surgery, rates of post-operative AF diagnosis have been reported ranging from 6 to 32%. Similar findings have resulted post-colorectal cancer resection. Although the true mechanism of this connection remains unknown, theories focus their etiology on the increased inflammatory state or hypercoagulability in cancer patients, as well as, tumor effect and co-morbid states. \textsuperscript{9,10} Few studies have researched the incidence of AF prior to cancer diagnosis for its potential screening use. This systematic review aims to assess the incidence of cancer diagnosis following new onset of AF and its potential utilization in preventative cancer screening.

**METHODS**

An exhaustive search of current literature was performed using MEDLINE-Ovid, CINAHL and Web of Science. Keywords used included: \textit{atrial fibrillation}, \textit{neoplasms} and \textit{risk}. Bibliographies of resulting studies were referenced for additional relevant studies. Articles selected for review were published in the English language, were exclusive to human subjects and observed AF preceding cancer diagnosis. Articles were assessed for quality using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE).\textsuperscript{11}

**RESULTS**

The literature search yielded a total of 202 studies. Duplicate studies were excluded and the remaining results were screened for relevance based on eligibility
criteria. Two observational cohort studies\textsuperscript{12,13} met the designated criteria for this systematic review, see Table I.

**Conen et al**

This prospective cohort study\textsuperscript{12} sought to investigate the increased risk for cancer in women newly diagnosed with AF. The study population included 34,691 women age 45 or greater previously enrolled in a randomized controlled trial of aspirin and vitamin E for the prevention of CV disease and cancer. Women were followed from enrollment in 1993 to 1995 through the end of the study period on March 31, 2004 with an optional additional observational cohort study. Women previously diagnosed with cancer, AF or major CV events were excluded from the cohort study. Those lost to follow up or who did not consent to the additional observational study were not included in this analysis. AF diagnosis was self-reported on questionnaires administered during the study period. For those who reported at least one episode of AF, medical records were reviewed and AF diagnosis confirmed by either electrocardiogram or medical documentation. Cancer was similarly self-reported on study questionnaires by participants with medical record review and confirmation via cytology, pathology or, if unavailable, by radiographic or laboratory evidence.\textsuperscript{12}

Primary endpoint for the study was invasive cancer with secondary outcomes of incidence of breast, colorectal and lung cancer. Considerations were made for the following: age, randomization assignment, education level, race, height, weight, hypertension, hypercholesterolemia, diabetes, smoking, alcohol use, physical activity, hormone replacement therapy, recent cancer screening and non fatal CV events. Demographics, risk factors and study outcomes were assessed via self-reported
questionnaire every 6 months during year one of follow up and every 12 months beyond. Cancer diagnosis was separated into 0-3 months, 3-12 months and greater than 12 months from the time of AF diagnosis. Risk of incident AF after new cancer diagnosis was also monitored, which is where the majority of previous research is focused. Two sensitivity analyses were performed and considered. One in which the adjustment for screening procedures was removed and the second where only incidence of AF diagnosed after 2006 were considered as this is when the AF validation process was initiated. The previous randomization was considered as well as a separate analysis performed utilizing only the randomized time period. Original study randomization therapies of ASA or vitamin E were not found to have significant effect on the outcome of AF or cancer.\textsuperscript{12}

During the study period 1467 women were diagnosed with new onset AF and 5130 with cancer. Those diagnosed with AF were found to be older, taller, had a greater BMI, higher prevalence of comorbidities, lower education level and were more likely to be Caucasian. Those diagnosed with cancer were found to have similar characteristics with the exclusion of education level and a higher incidence of smoking. Of those diagnosed with cancer 147 (10%) had a preceding AF diagnosis. The incidence of cancer was 0.8 per 100 among those without an AF diagnosis versus 1.4 per 100 person-years of follow-up in those with an AF diagnosis. The multi variable adjustment hazard ratio (HR) for AF association with cancer was 1.48; 95\% CI, 1.25-1.75; P < .001. The randomization therapies were not found to have an impact on these results, P = .27 and .16 for interaction via subdistribution hazard models. Risk of cancer was found to be highest within the first 3 months of AF diagnosis (Adjusted HR, 3.5; 95\% CI, 2.05-6.10;
P < .001), the risk remained increased beyond 1-year post diagnosis (Adjusted HR 1.42; 95% CI, 1.18-1.71; P < .001). Analysis of cancer types revealed the highest association between new onset AF and colon cancer.\textsuperscript{12}

The authors acknowledge the possibility of detection bias as women diagnosed with new onset AF were more exposed to healthcare and therefore had access to screenings and detection of disease. Colon cancer discovery as a result of increased colorectal bleeding caused by anticoagulants used to treat AF was additionally recognized as possible detection bias. Cancer screening measures were not increased in patients diagnosed with AF nor did an adjustment for screening affect the resulting statistics. Strengths of this study included the large population size and the length of time for which data remained available with minimal missing information. The authors accounted for many possible confounders in their statistical analysis with consistent outcomes.\textsuperscript{12}

\textbf{Oatenfeld et al}

This prospective cohort study\textsuperscript{13} observed the Danish population from January 1, 1980 through December 31, 2011. The Danish National Registry of Patients was utilized to identify all persons with new diagnosis of AF. The method of identification was based on ICD-8 codes until the ICD-9 codes were established in 1993. Researchers further collected data on comorbidities of those diagnosed with AF including diabetes, hyperthyroidism, COPD, alcoholism and surgeries within 3 months of AF diagnosis. These comorbidities were ranked based on the Charlson score as low, medium or high. To determine cancer risk, the Danish Cancer Registry was utilized to link any citizen diagnosed with new onset AF with a cancer diagnosis if one was present. Data collected
included cancer stage at diagnosis and the degree of metastatic versus localized cancers. Any person diagnosed with cancer prior to their AF diagnosis was excluded from the study.13

Patients were followed from the time of their AF diagnosis to study endpoint, death or emigration. Cancer risk was gauged via Statistical Information on Recidivism (SIR) by comparing cancer risk amongst study patients diagnosed with AF versus expected risk within the Danish population. Expected risk was based on national incidence and quantified as though those in the study had the same risk as the general population. During the study period 269,742 patients were diagnosed with new onset AF. Of those 6656 patients were diagnosed with cancer resulting in an absolute risk of 2.5% (95% CI, 2.4%-2.5%). There were no significant differences between genders or age groups, except for a lower relative risk amongst the 0-29 year group (0.95%; 95% CI, 0.63-2.38). At the 3-month follow up visit the SIR was 5.11% (95% CI, 4.99 – 5.24). Beyond the 3-month follow up cancer risk remained increased, however, continued to decrease over time. The most prevalent cancers were lung, kidney and colon. An increased risk of non-Hodgkin lymphoma as well as cancers associated with obesity and smoking were also observed. Information on cancer spread was available for 26,528 of the 34,962 patients in the study. Within 3 months of follow up for new onset AF, metastatic cancer was diagnosed in 2848 compared to the expected 406 (SIR, 7.02; 95% CI, 6.76 – 7.28). Localized cancer was diagnosed in 2129 patients compared to the expected 603 (SIR 3.53; 95% CI, 3.38- 3.68). In an analysis limited to the patients with AF as the primary diagnosis, 2365 cancers were diagnosed within the first 3 months of AF diagnosis compared to the expected 757 cases (SIR 3.13%; 95% CI, 3.00-3.25) with
an absolute risk of 1.5% (95%CI, 1.4-1.5). When further excluding patients who received both diagnoses at the same visit the 3-month SIR was 1.63% (95%CI, 1.56-1.7) with an absolute risk of 0.8% (95% CI, .77%- .84%).

Authors of this study concluded that it was likely that occult cancer was already present at the time of AF diagnosis, as previous research has indicated; however, researches believe new onset AF may be the first indicator of occult cancer. The strengths of this study included the population-based design under the tax-supported health system of Denmark. Authors believe limitations of the study may include coding errors within the registry or errors leading to overestimation of risk. Despite these limitations it was concluded that the relative risks may be underestimated based on exclusions made during analysis and removal of data on patients diagnosed with AF and cancer at the same visit.

**DISCUSSION**

While previous studies have demonstrated a significant risk for AF after cancer diagnosis or during cancer treatment, few have looked at the risk of cancer diagnosis after new onset AF. This systematic review was able to identify two published articles that addressed the question of whether or not new onset AF may be an indicator of undiagnosed cancer. Both articles acknowledge the possibility of detection bias based on heath care access as well as possible overestimation of risk. These studies were evaluated via the GRADE method, results can be found in Table I.

These studies conclusively established an increased risk of cancer in those individuals newly diagnosed with AF, specifically for colon and lung cancer, 2 of the top 3 leading causes of cancer deaths in the United States. The greatest incidence of
cancer diagnosis in both populations studied is recognized to be within 0-3 months following new AF diagnosis with a lasting increased risk for up to the first 12 months after diagnosis.\textsuperscript{12,13} Ostenfeld et al\textsuperscript{13} additionally found an increased risk for non-Hodgkin lymphoma and kidney cancer versus Conen et al\textsuperscript{12} found an additional increased risk for breast cancer. The increased breast cancer risk is likely due to population bias as this study observed only women. There is a strong possible detection bias in diagnosis of colon cancer in those with AF who are treated with anticoagulants as there is an increased risk of gastrointestinal bleed with such therapies warranting medical exploration and likely detection of colon cancer if present; this is acknowledged by researchers in both articles.

AF is diagnosed via a non-invasive and cost effective electrocardiogram tracing while a cancer diagnosis may consist of a series of labs and often an invasive biopsy. To screen every individual newly diagnosed with AF for cancer would be an enormous cost burden and result in unnecessary invasive procedures. It may be reasonable for those with an increased risk of colorectal, breast, or lung cancer who develop AF to aggressively pursue risk factor reduction with baseline minimally invasive tumor marker laboratory tests to monitor for potential cancer development.

According to the CDC, colorectal cancer is the second leading cause of cancer related death with lung cancer being the first amongst men and women in the United States.\textsuperscript{8} A prospective study\textsuperscript{14} conducted on a Veteran’s Affairs (VA) population investigating diseases that precede colon cancer found a significant increase in AF diagnosis prior to colon cancer diagnosis with an odds ratio of 1.34; 95\%CI 1.16-1.55. In follow up to the VA study, a case control study\textsuperscript{15} was performed in Italy observing the
incidence of AF among 456 patients diagnosed with colon cancer compared to a control group of 791 patients without colon cancer. This study found that 5% of the patients diagnosed with colon cancer had an established diagnosis of AF versus 2% of the control group. This revealed a more than double the incidence of AF among patients diagnosed with colon cancer. It is hypothesized that occult cancer is already present at the time of AF diagnosis and that AF may be the earliest indicator.

In addition, the REASONS prospective cohort study analyzed a population of individuals living in North Carolina, South Carolina, Georgia, Alabama, Mississippi, Tennessee, Arkansas and Louisiana to observe racial and regional cause of stroke. A sub-analysis of this information divided the study population into subgroups to including age, race, gender, CV risk factor and inflammatory marker measurements. A total of 15,428 individuals qualified for this sub-analysis in which participants were then placed into AF or no AF groups as well as cancer or no cancer groups. Figure I graphically depicts the results which show a higher incidence of cancer in those diagnosed with AF across all subgroups.

Cancer and AF have several shared risk factors including age, smoking, obesity and metabolic disorders. There are several theories as to the connection between AF and cancer of which the most widely agreed upon is the increased inflammatory state associated with both AF and cancer; however, in general the mechanism of AF remains inadequately understood. Future research is warranted as this systematic review demonstrates an established increased risk of cancer in those diagnosed with new-onset-AF specifically the leading causes of cancer death: lung, breast and colorectal. While theories exist as to the physiologic connection between AF and cancer
there is no widely accepted theory. A true understanding of the mechanism connecting these disease states would provide a platform for preventative screening and possible therapies. A large study observing a diverse population is required to validate these findings. The articles addressed in this review had populations limited to the primarily Caucasian population of Denmark\textsuperscript{13} and an all female population.\textsuperscript{12}

CONCLUSION

The studies evaluated in this systematic review revealed a significant increased incidence in cancer diagnosis amongst those diagnosed with new onset AF. While both studies observed the risk increased specifically in colon and lung cancer, the populations were not able to be compared directly as Conen et al\textsuperscript{12} observed only females while Ostenfeld et al\textsuperscript{13} observed an entire primarily Caucasian country’s population. Through larger diverse population observational studies, new onset AF has the potential to become recognized as an important risk factor in the screening for cancer.
References


Table I: Quality Assessment of Reviewed Studies

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<td>Ostenfeld et al\textsuperscript{13}</td>
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\textsuperscript{a} Both studies considered all reasonable confounders and multivariable adjusted their risk calculations based on any possibility of demographic or exposure bias with a significant risk remaining despite these considerations.

Figure I: Prevalence of AF in Sub-Groups of Cancer vs. Non-Cancer Patients

O’Neal et al\textsuperscript{16} 2015