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Original Contribution

The Associations of Atrial Fibrillation With the Risks of Incident Invasive Breast and Colorectal Cancers

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Atrial fibrillation (AF) is a common arrhythmia that poses a significant risk of stroke. Cross-sectional and case-control studies have shown evidence of associations between AF and breast or colorectal cancer, but there have been no longitudinal studies in which this has been assessed. We prospectively examined a cohort of 93,676 postmenopausal women enrolled in the Women's Health Initiative from 1994 to 1998 to determine whether there are relationships between baseline AF and the development of invasive breast or colorectal cancer. The prevalence of self-reported physician diagnosis of AF at baseline was 5.1%. Over approximately 15 years of follow-up, the incidence of invasive breast cancer was 5.7%, and the incidence of colorectal cancer was 1.6%. Adjusted hazard ratios and 95% confidence intervals were obtained using Cox proportional hazards models. We found no significant association between AF and incident colorectal cancer, but we did see a 19% excess risk of invasive breast cancer among those with AF (adjusted hazard ratio (HR) = 1.19, 95% confidence interval (CI): 1.03, 1.38). Additional adjustment for baseline use of cardiac glycosides attenuated the association between AF and invasive breast cancer (HR = 1.01, 95% CI: 0.85, 1.20). Cardiac glycoside use was strongly associated with incident invasive breast cancer (HR = 1.68, 95% CI: 1.33, 2.12) independent of AF and other confounders. Mechanisms of the associations among breast cancer, AF, and cardiac glycosides need further investigation.

atrial fibrillation; breast cancer; colorectal cancer; cardiac glycosides; digoxin

Abbreviations: AF, atrial fibrillation; CI, confidence interval; ECG, electrocardiogram; HR, hazard ratio; WHI, Women's Health Initiative.

Atrial fibrillation (AF) is the most common clinically significant cardiac arrhythmia. It occurs in approximately 1% of the general population, and the prevalence increases substantially with age to approximately 7% in persons 60–69 years of age and 13% in persons older than 80 years (1). AF is a significant risk factor for stroke and heart failure. Primarily associated with cardiovascular conditions such as hypertension, coronary artery disease, myocardial infarction, hearth failure, and valvular disease, AF shares some characteristics and co-exists with many noncardiac conditions (2). Very few data currently exist on possible relationships between AF and malignant diseases.

There have been 2 studies thus far in which investigators have reported a higher risk of AF diagnosis in cancer patients. In 1994, Müller et al. (3) published a case-control study of nonsteroidal antiinflammatory drug treatment among 12,304 veterans with a primary diagnosis of colon cancer; they described as a secondary finding that AF and atrial flutter were associated with an increased occurrence of colon cancer after 5–10 years. More recently, in 2008, Guzzetti et al. (4) reported an at least 2- to 3-fold higher prevalence of AF among subjects with either colorectal or breast cancer cases than among controls who did not have cancer. Several mechanisms for this association have been postulated. For example,

inflammation is thought to play a role because of the observed elevation of inflammatory markers in AF and carcinogenesis (5–7). There have been no prospective studies of the relationships of AF with incident cancers.

The Women's Health Initiative (WHI) Observational Study, an ongoing prospective study of 93,676 postmenopausal women with long-term follow-up, addresses the roles of biologic and lifestyle factors in the common causes of morbidity, mortality, and impaired quality of life in postmenopausal women (8). This study provides an excellent opportunity to examine the prospective associations of AF with breast cancer and colorectal cancer after controlling for potential confounders.

METHODS

The WHI Observational Study, which was sponsored by National Heart, Lung, and Blood Institute, enrolled 93,676 women 50–79 years of age in 40 centers throughout the United States during the years 1994–1998. The study design and baseline characteristics of participants have been described in detail elsewhere (8). In brief, participants were recruited through mass mailings to voter registration, motor vehicle registration, and commercial lists or were women who did not wish to join or were not eligible for the WHI clinical trials of hormone therapy or dietary modification. Participants completed multiple questionnaires about their physical and mental health and comorbid conditions and had a baseline clinic visit during which they had physical measurements (weight, height, waist-hip measurements, blood pressure) taken and a fasting blood draw. Participants brought in their medications in original pill bottles, and the labels were scanned and entered into a medications database. Three years after the baseline visit, women had another clinic visit, at which time the same measurements were obtained and questionnaires administered. All research activities were approved by the institutional review boards of all involved institutions, and all participants in the WHI provided written informed consent.

Outcomes ascertainment

Annual follow-up was conducted using mailed questionnaires and telephone calls to determine hospitalizations and potential outcome events. When a hospitalization occurred, medical records were obtained from the hospital and outside providers. Outcomes packets were then prepared for adjudication of events by local study physicians and subsequently sent to the WHI coordinating center in Seattle, Washington, for central adjudication and coding of breast cancer stage, size, nodal status, grade, histology, and estrogen receptor and progesterone receptor status. Of the 93,676 women in the observational study, 471 (0.5%) had missing data on follow-up time and were excluded from these analyses. Incident breast cancer was defined as no history of any type of breast cancer at baseline, no evidence of in situ breast cancer on follow-up, and a diagnosis of breast cancer (invasive) during follow-up. Similarly, incident colorectal cancer was defined as no history of colorectal cancer at baseline and a diagnosis of colorectal cancer during follow-up.

Definition of AF

In the WHI Observational Study, information on AF was ascertained from annual self-reports of AF diagnosis. One problem in research on AF is that because it may be paroxysmal or intermittent, relying on diagnoses from electrocardiograms (ECGs) results in underestimation of the prevalence. Risks of cerebrovascular events associated with AF are similar for those with persistent or intermittent AF, and many patients who initially present with paroxysmal AF often progress to persistent or more recurrent AF (9–11). Further, based on the results of the Reasons for Geographic and Racial Differences in Stroke (REGARDS) Study (12), self-reported AF is a strong predictor of stroke and can be used interchangeably with an ECG diagnosis of AF in models predicting risk. The sensitivity of ECG diagnosis is lower than that for self-report, but the specificity is higher. Thus, using self-reported histories of physician-diagnosed AF might lead to better estimates of prevalence than using results from individual ECGs. Although only self-reported data are available in the WHI Observational Study, we can draw inferences about the sensitivity of self-report versus ECG diagnosis from the clinical trial of the WHI, in which there were both ECG and self-reported data on AF. In the clinical trial, the prevalence of AF on baseline ECG was 0.3% (184 of 66,777 women in the clinical trial with non-missing ECGs). Among those who had an ECG diagnosis of AF, 80.2% self-reported a physician's diagnosis compared with 3.7% of those who did not have AF on baseline ECG, indicating that the vast majority of women with ECG-documented AF were aware of it. Among 2,589 women who self-reported a diagnosis of AF in the clinical trial, 146 (5.6%) also had a baseline ECG diagnosis of AF compared with 36 of 63,020 (0.06%) of those who did not self-report AF, indicating that a single screening ECG did not capture the large majority of women with AF. In the present study, use of the self-reported physician diagnosis of AF may tend to lead to inclusion of women without AF in the AF group, but it is not likely to include women with AF in the non-AF group, thus providing conservative estimates of relationships.

In order to further reduce potential ascertainment bias, we considered a woman to have AF if she self-reported a physician diagnosis of AF at baseline regardless of her self-reports on follow-up questionnaires. We considered a woman to be in the no-AF group if she did not report AF at baseline and did not report it at any of the follow-up visits/questionnaires. Those with missing responses to the AF question ($n = 1{,}531$) and those who did not report AF at baseline but did report it in 1 of the follow-up visits ($n = 5{,}628$) were excluded from all analyses, resulting in a total sample size of 86,046 women with valid AF data.

Statistical analysis

Comparisons of baseline characteristics between women with and without AF, between with incident invasive breast cancer and those with no breast cancer, and between women with incident colorectal cancer and those with no colorectal cancer were done using χ^2 tests for categorical variables and Student's t test for continuous variables. Cox proportional

Table 1. Baseline Characteristics of Study Participants, by Atrial Fibrillation Status at Baseline, Women's Health Initiative Observational Study, 1994–1998

Characteristic	Atrial Fibrillation at Baseline (n = 4,376)			No Atrial Fibrillation at Baseline (n = 81,670)			*P* Value
	Mean (SD)	No.[a]	%	Mean	No.[a]	%	
Age, years	66.9 (7.1)			63.2 (7.3)			<0.001
BMI[b]	27.4 (6.0)			27.2 (5.8)			0.04
Age at menopause, years	47.1 (7.1)			47.5 (6.6)			<0.01
Resting pulse (30 seconds)	34.1 (6.3)			34.7 (6.1)			<0.001
Ethnicity							<0.001
Non-Hispanic white		3,687	84.5		67,895	83.4	
Black		393	9.0		6,658	8.2	
Hispanic/Latino		115	2.6		3,195	3.9	
Other		170	3.9		3,688	4.5	
Educational level							<0.001
<College degree		2,852	65.6		46,448	57.3	
≥College degree		1,498	34.4		34,552	42.7	
Income							<0.001
<$20,000		949	23.6		11,687	15.4	
$2,000–$49,999		1,867	46.4		32,580	43.0	
$50,000–$74,999		658	16.4		15,564	20.6	
≥$75,000		551	13.7		15,924	21.0	
Marital status							<0.001
Never married		205	4.7		3,828	4.7	
Divorced/separated		649	14.9		12,919	15.9	
Widowed		1,027	23.6		13,667	16.8	
Married/living such		2,476	56.8		50,858	62.6	
Smoking status							0.19
Never smoker		2,224	51.7		41,135	51.0	
Past smoker		1,837	42.7		34,417	42.7	
Current smoker		244	5.7		5,116	6.3	
Physical activity level							<0.001
No activity		690	16.0		10,813	13.4	
Mild		1,795	41.7		30,858	38.1	
Moderate		777	18.0		15,005	18.6	
Strenuous		1,048	24.3		24,230	30.0	
Age at menarche, years							0.02
≤10		296	6.8		5,322	6.5	
11–13		2,991	68.6		57,656	70.8	
14–15		886	20.3		15,205	18.7	
≥16		188	4.6		3,282	4.0	
Age at first birth, years							0.04
No term pregnancy		524	13.3		10,476	14.2	
<20		538	13.7		9,121	12.4	
20–29		2,516	64.0		47,758	64.9	
≥30		352	9.0		6,278	8.5	
Parity							<0.001
No term pregnancy		524	12.0		10,476	12.9	
1		378	8.7		7,477	9.2	
2–3		2,114	48.6		41,146	50.7	
≥4		1,337	30.7		22,121	27.2	

Table continues

Table 1. Continued

Characteristic	Atrial Fibrillation at Baseline (n = 4,376)			No Atrial Fibrillation at Baseline (n = 81,670)			*P* Value
	Mean (SD)	No.[a]	%	Mean	No.[a]	%	
Hormone therapy use							<0.001
Never		1,755	40.1		33,167	40.7	
Past		824	18.9		11,838	14.5	
Current		1,793	41.0		36,590	44.8	
Hysterectomy							<0.001
No		2,176	49.8		48,188	59.1	
Yes		2,193	50.2		33,413	41.0	
Hypertension							<0.001
Nonhypertensive		2,243	52.7		54,836	68.1	
Untreated		441	10.4		6,183	7.7	
Treated		1,570	36.9		19,533	24.3	
Diabetes (treated)							<0.001
No		4,045	92.6		78,370	96.1	
Yes		325	7.4		3,199	3.9	
High cholesterol requiring medication							
No		3,366	78.8		68,583	85.5	
Yes		905	21.2		11,612	14.5	
History of CVD							<0.001
No		3,029	69.2		75,065	91.9	
Yes		1,347	30.8		6,605	8.1	
History of CHF							<0.001
No		4,104	93.8		81,179	99.4	
Yes		272	6.2		486	0.6	
Warfarin use							<0.001
No		3,785	86.5		81,269	99.5	
Yes		591	13.5		400	0.5	
Anti-arrhythmic use							<0.001
No		4,091	93.5		81,594	99.9	
Yes		285	6.5		75	0.1	
Aspirin use							<0.001
No		2,923	66.8		63,358	77.6	
Yes		1,453	33.2		18,311	22.4	
Statin use							<0.01
No		3,859	88.2		75,212	92.1	
Yes		517	11.8		6,457	7.9	
β-blocker use							<0.001
No		3,335	76.2		75,567	92.5	
Yes		1,041	23.8		6,103	7.5	
Calcium channel blocker use							
No		3,425	78.3		74,285	91.0	
Yes		951	21.7		7,385	9.0	
ACE inhibitor use							<0.001
No		3,804	86.9		75,468	92.4	
Yes		572	13.1		6,202	7.6	

Table continues

Table 1. Continued

Characteristic	Atrial Fibrillation at Baseline (n = 4,376)			No Atrial Fibrillation at Baseline (n = 81,670)			*P* Value
	Mean (SD)	No.[a]	%	Mean	No.[a]	%	
Angiotensin II receptor blocker use							<0.001
No		4,314	98.6		81,090	99.3	
Yes		62	1.4		580	0.7	
Cardiac glycoside use							<0.001
No		3,137	71.7		81,175	99.4	
Yes		1,239	28.3		494	0.6	

Abbreviations: ACE, angiotensin-converting enzyme; BMI, body mass index; CHF, congestive heart failure; CVD, cardiovascular disease; SD, standard deviation.

[a] Subgroup totals may not sum to the column total because of missing data.

[b] Weight (kg)/height (m)^2.

hazards models were run to obtain hazard ratios and 95% confidence intervals for the associations of self-reported AF with incident invasive breast cancer and colorectal cancer. Variables that were associated with both AF prevalence and incident invasive breast cancer were considered potential confounders in breast cancer regression analyses and were used as adjustment factors. Similarly, variables associated with both AF prevalence and incident colorectal cancer were used as adjustment variables in analyses pertaining to colorectal cancer. For the outcome of invasive breast cancer, parity and age at first birth were both potential confounders; however, because of collinearity, only one could be retained in multivariable analyses. Serial adjustment for either parity or age at first birth resulted in similar estimates of risk, so we report models adjusted for parity because parity data were missing for fewer participants. Patients with a history of breast cancer at baseline or a missing response to that question (n = 5,400), as well as those who were diagnosed with in situ breast cancer (n = 1,016) or whose type of breast cancer was unknown (n = 43), were excluded from the breast cancer analyses, and patients with a history of colorectal cancer or missing data at baseline (n = 1,338) were excluded from the colorectal cancer analyses. For both outcomes separately, we ran Cox regression models that were unadjusted, adjusted for age and race, and adjusted for age, race, and cancer-specific potential confounders. Missing data were minimal (<1.8%) for all adjustment variables except for age at menopause and income, which were missing on approximately 7%–10% of the sample. However, estimates from unadjusted and minimally adjusted models were virtually identical regardless of whether complete case analysis for the fullest model was applied or not; therefore, we report results from all models restricted to participants with complete covariate data based on the fullest adjustment to allow for direct comparison of estimates from unadjusted to adjusted models. We also conducted several sensitivity analyses in which we excluded women who self-reported congestive heart failure at baseline (for both invasive breast cancer and colorectal cancer); evaluated AF and cardiac glycoside use as time-varying variables in models in which invasive breast cancer was the outcome; and stratified models of invasive breast cancer by estrogen receptor status. In the time-varying analyses, we incorporated information about self-reported AF and cardiac glycoside use at baseline and at year 3. There was no evidence of violations of the assumption of proportional hazards in any of the regression models reported. All reported P values are 2-sided, and $P < 0.05$ was considered statistically significant. Statistical analyses were conducted with STATA, version 14 (StataCorp LP, College Station, Texas).

RESULTS

The prevalence of self-reported physician diagnosis of AF at baseline in the analytic sample was 5.1% (4,376 of 86,046). The incidence of invasive breast cancer during follow-up was 5.7% (4,497 of 79,587). Median follow-up time for breast cancer analyses was 15.3 years (interquartile range, 8.1–17.1). The incidence of colorectal cancer was 1.6% (1,373 of 84,708), with a median follow-up time of 15.9 years (interquartile range, 8.5–17.4). Tables 1–3 compare baseline characteristics of participants with AF, breast cancer, or colorectal cancer with characteristics of those without these conditions. Because of the large numbers, many (but not all) baseline variables were statistically significantly different among the AF, breast cancer, and colorectal cancer groups.

Women with AF at baseline had a significantly higher risk of invasive breast cancer (hazard ratio (HR) = 1.23, 95% confidence interval (CI): 1.06, 1.42) in unadjusted analyses (Table 4). The excess risk remained after adjustment for age and race (HR = 1.19, 95% CI: 1.03, 1.37) and further adjustment for educational level, income, marital status, physical activity level, parity, age at menopause, hormone therapy use, hysterectomy, diabetes, and history of cardiovascular disease (myocardial infarction, stroke, transient ischemic attack, angina, or revascularization) (HR = 1.19, 95% CI: 1.03, 1.38). Use of warfarin, anti-arrhythmic drugs,

Table 2. Baseline Characteristics of Study Participants, by Incident Invasive Breast Cancer Status, Women's Health Initiative Observational Study, 1994–1998

Characteristic	Incident Invasive Breast Cancer (n = 4,497)			No Incident Invasive Breast Cancer (n = 75,090)			*P* Value
	Mean (SD)	No.[a]	%	Mean (SD)	No.[a]	%	
Age, years	63.3 (7.1)			63.3 (7.4)			0.47
BMI[b]	27.3 (5.7)			27.2 (5.9)			0.27
Age at menopause, years	48.4 (6.6)			47.4 (6.7)			<0.001
Resting pulse (30 seconds)	34.8 (6.1)			34.6 (6.0)			0.24
Ethnicity							<0.001
Non-Hispanic white		4,015	89.5		62,076	82.9	
Black		226	5.0		6,247	8.3	
Hispanic/Latino		102	2.3		3,023	4.0	
Other		144	3.2		3,534	4.7	
Educational level							<0.001
<College degree		2,309	51.7		43,422	58.3	
≥College degree		2,161	48.3		31,050	41.7	
Income							<0.001
<$20,000		514	12.3		11,191	16.1	
$20,000–$49,999		1,775	42.4		30,067	43.2	
$50,000–$74,999		925	22.1		14,064	20.2	
≥$75,000		976	23.3		14,264	20.5	
Marital status							0.001
Never married		231	5.2		3,417	4.6	
Divorced/separated		667	14.9		11,948	16.0	
Widowed		691	15.4		12,762	17.1	
Married/living such		2,891	64.5		46,595	62.4	
Smoking status							<0.001
Never smoker		2,141	48.1		38,080	51.4	
Past smoker		2,035	45.7		31,344	42.3	
Current smoker		274	6.2		4,735	6.4	
Physical activity level							0.03
No activity		552	12.4		10,095	13.6	
Mild		1,663	37.4		28,519	38.3	
Moderate		864	19.4		13,697	18.4	
Strenuous		1,372	30.8		22,086	29.7	
Age at menarche, years							0.11
≤10		323	7.2		4,880	6.5	
11–13		3,189	71.1		52,889	70.6	
14–15		796	17.8		14,088	18.8	
≥16		175	3.9		3,057	4.1	
Age at first birth, years							<0.001
No term pregnancy		657	15.8		9,349	13.8	
<20		413	9.9		8,651	12.8	
20–29		2,672	64.3		43,991	65.1	
≥30		411	9.9		5,606	8.3	
Parity							<0.001
No term pregnancy		657	14.7		9,349	12.5	
1		415	9.3		6,794	9.1	
2–3		2,313	51.7		37,718	50.5	
≥4		1,088	24.3		20,819	27.9	

Table continues

Table 2. Continued

Characteristic	Incident Invasive Breast Cancer (n = 4,497)			No Incident Invasive Breast Cancer (n = 75,090)			*P* Value
	Mean (SD)	No.[a]	%	Mean (SD)	No.[a]	%	
Hormone therapy use							<0.001
Never		1,541	34.3		29,883	39.8	
Past		565	12.6		10,349	13.8	
Current		2,384	53.1		34,792	46.4	
Hysterectomy							<0.001
No		2,829	63.0		43,844	58.4	
Yes		1,664	37.0		31,176	41.6	
Hypertension							0.31
Nonhypertensive		3,022	68.1		49,860	67.3	
Untreated		323	7.3		5,840	7.9	
Treated		1,093	24.6		18,353	24.8	
Diabetes (treated)							<0.001
No		4,359	97.0		71,881	95.9	
Yes		135	3.0		3,113	4.2	
High cholesterol requiring medication							0.15
No		3,791	86.0		62,877	85.3	
Yes		615	14.0		10,874	14.7	
History of CVD							<0.02
No		4,130	91.8		68,169	90.8	
Yes		367	8.2		6,921	9.2	
History of CHF							0.64
No		4,455	99.1		74,435	99.1	
Yes		42	0.9		651	0.9	
Warfarin use							0.22
No		4,438	98.7		74,254	98.9	
Yes		59	1.3		835	1.1	
Anti-arrhythmic use							0.29
No		4,474	99.5		74,783	99.6	
Yes		23	0.5		306	0.4	
Aspirin use							0.18
No		3,428	76.2		57,897	77.1	
Yes		1,069	23.8		17,192	22.9	
Statin use							0.25
No		4,157	92.4		69,054	92.0	
Yes		340	7.6		6,035	8.0	
β-blocker use							0.35
No		4,107	91.3		68,876	91.7	
Yes		390	8.7		6,214	8.3	
Calcium channel blocker use							0.95
No		4,065	90.4		67,853	90.4	
Yes		432	9.6		7,237	9.6	
ACE inhibitor use							0.44
No		4,159	92.5		69,207	92.2	
Yes		338	7.5		5,883	7.8	

Table continues

Table 2. Continued

Characteristic	Incident Invasive Breast Cancer (n = 4,497)			No Incident Invasive Breast Cancer (n = 75,090)			*P* Value
	Mean (SD)	No.[a]	%	Mean (SD)	No.[a]	%	
Angiotensin II receptor blocker use							0.80
No		4,465	99.3		74,530	99.3	
Yes		32	0.7		560	0.7	
Cardiac glycoside use							<0.001
No		4,372	97.2		76,654	98.1	
Yes		125	2.8		1,435	1.9	

Abbreviations: ACE, angiotensin-converting enzyme; BMI, body mass index; CHF, congestive heart failure; CVD, cardiovascular disease; SD, standard deviation.

[a] Subgroup totals may not sum to the column total because of missing data.

[b] Weight (kg)/height (m)^2.

β-blockers, aspirin, statins, calcium channel blockers, or angiotensin II receptor blockers was not related to breast cancer; however, baseline use of cardiac glycosides was associated with a 68% higher risk of invasive breast cancer (HR = 1.68, 95% CI: 1.33, 2.12) after adjustment for other potential confounders. When we considered only women with estrogen receptor–positive tumors (n = 2,994), the hazard ratio for cardiac glycosides was 1.75 (95% CI: 1.34, 2.27). The hazard ratio among women with estrogen receptor–negative tumors (n = 511) was not significant (HR = 1.33, 95% CI: 0.68, 2.62). There were 231 women in our analytic cohort with invasive breast cancer who had missing assays. When we included cardiac glycosides in the Cox model, the association of AF with breast cancer was attenuated to a hazard ratio of 1.01 (95% CI: 0.85, 1.20). There was no significant association of baseline AF with colorectal cancer in either unadjusted or adjusted analyses. Cardiac glycoside use was not associated with the risk colorectal cancer (adjusted HR = 1.08, 95% CI: 0.71, 1.64).

We further investigated the association of AF with breast cancer in relation to cardiac glycoside use by categorizing women into 4 mutually exclusive groups based on their self-reported baseline AF status and self-reported cardiac glycoside medication use at baseline. Compared with women who did not have AF and were not taking cardiac glycosides, women with AF who were not taking cardiac glycosides did not have a higher risk of breast cancer (HR = 1.01, 95% CI: 0.85, 1.20) in adjusted analyses (Table 5). Women taking cardiac glycosides at baseline, regardless of whether they reported AF or no AF at baseline, had a significantly increased risk of breast cancer on follow-up (for AF, HR = 1.70, 95% CI: 1.35, 2.13; for no AF, HR = 1.69, 95% CI: 1.13, 2.50)

Similar results were found for both outcomes in sensitivity analysis in which we restricted the sample to those without prevalent congestive heart failure (n = 663 for breast cancer analyses and n = 779 for colorectal cancer analyses; data not shown). AF was associated with an increased risk of breast cancer that was attenuated after adjustment for cardiac glycoside use, and no significant difference in risk was seen for colorectal cancer in adjusted or unadjusted analyses. In analyses of invasive breast cancer in which both AF and cardiac glycoside use were treated as time-varying variables, the results were similar. Findings for women with estrogen receptor–positive tumors (n = 2,994) were similar to those for women with all types of invasive breast cancer. There were only 511 women with estrogen receptor–negative tumors, so the nonsignificant findings in that group may reflect low power. The remainder of the breast cancer case patients had missing assays.

DISCUSSION

In a large prospective study of postmenopausal women 50–79 years of age, we found that AF in older women was associated with a 19% higher risk of incident breast cancer after adjustment for multiple variables; however, this association was explained by use of cardiac glycosides at baseline. In our study, there was no relationship between AF and colorectal cancer incidence.

Studies of AF can be challenging because AF can be paroxysmal (self-terminating), persistent (sustained greater than 7 days), or permanent (typically greater than 1 year and when cardioversion has failed or is foregone). For the purposes of our study, we considered self-reported clinical diagnoses of AF to provide a more relevant estimate of the true prevalence of all types of AF than a 1-time ECG diagnosis. In a retrospective case-control study by Guzzetti et al. (4) in which AF was determined using a presurgical ECG, the authors observed a prevalence of AF that was at least 2 times higher in both patients with breast cancer and those with colorectal cancer than in control subjects, which raises the interesting question of whether AF precedes or follows cancers. Analyses of our data suggest that there is no association of incidence of breast cancer or colorectal cancer following a baseline diagnosis of AF after controlling for important confounders.

Although our results indicated a higher risk of breast cancer in women with prevalent AF even after adjustment for age, race, and cardiovascular comorbid conditions or risk factors for heart diseases, further adjustment for use of

Table 3. Baseline Characteristics of Study Participants, by Incident Colorectal Cancer Status, Women's Health Initiative, 1994–1998

Characteristic	Incident Colorectal Cancer (n = 1,373)			No Incident Colorectal Cancer (n = 83,335)			*P* Value
	Mean (SD)	No.[a]	%	Mean (SD)	No.[a]	%	
Age, years	66.1 (7.0)			63.3 (7.3)			<0.001
BMI[b]	27.9 (5.8)			27.2 (5.8)			<0.001
Age at menopause, years	47.8 (6.7)			47.4 (6.6)			0.06
Resting pulse (30 seconds)	35.1 (6.6)			34.7 (6.1)			0.02
Ethnicity							<0.01
Non-Hispanic white		1,171	85.4		69,332	83.4	
Black		122	8.9		6,786	8.2	
Hispanic/Latino		32	2.3		3,220	3.9	
Other		46	3.4		3,760	4.5	
Educational level							0.07
<College degree		820	60.0		47,633	57.6	
≥College degree		546	40.0		35,029	42.4	
Income							<0.001
<$20,000		235	18.3		12,126	15.7	
$20,000–$49,999		623	48.5		33,275	43.1	
$50,000–$74,999		229	17.8		15,765	20.4	
≥$75,000		197	15.3		16,119	20.9	
Marital status							<0.001
Never married		69	5.0		3,894	4.7	
Divorced/separated		216	15.8		13,140	15.8	
Widowed		297	21.7		14,082	17.0	
Married/living such		787	57.5		51,817	62.5	
Smoking status							0.04
Never smoker		652	48.1		42,102	51.2	
Past smoker		602	44.4		35,037	42.6	
Current smoker		101	7.5		5,173	6.3	
Physical activity level							<0.01
No activity		219	16.1		11,095	13.4	
Mild		540	39.7		31,553	38.2	
Moderate		250	18.4		15,311	18.5	
Strenuous		353	25.9		24,628	29.8	
Age at menarche, years							0.19
≤10		109	8.0		5,432	6.5	
11–13		946	69.0		58,768	70.7	
14–15		261	19.0		15,570	18.7	
≥16		55	4.0		3,366	4.1	
Age at first birth, years							0.82
No term pregnancy		178	14.3		10,634	14.2	
<20		153	12.3		9,351	12.4	
20–29		797	64.1		48,768	64.9	
≥30		115	9.3		6,403	8.5	
Parity							0.03
No term pregnancy		178	13.0		10,634	12.8	
1		129	9.4		7,589	9.2	
2–3		642	47.0		42,008	50.7	
≥4		418	30.6		22,660	27.3	

Table continues

Table 3. Continued

Characteristic	Incident Colorectal Cancer (n = 1,373)			No Incident Colorectal Cancer (n = 83,335)			*P* Value
	Mean (SD)	No.[a]	%	Mean (SD)	No.[a]	%	
Hormone therapy use							<0.001
Never		674	49.2		33,616	40.4	
Past		226	16.5		12,217	14.7	
Current		471	34.4		37,428	45.0	
Hysterectomy							0.52
No		794	57.8		48,869	58.7	
Yes		579	42.2		34,390	41.3	
Hypertension							0.01
Nonhypertensive		862	63.7		55,459	67.5	
Untreated		111	8.2		6,400	7.8	
Treated		381	28.1		20,355	24.8	
Diabetes (treated)							0.01
No		1,298	94.6		79,857	96.0	
Yes		74	5.4		3,374	4.1	
High cholesterol requiring medication							0.08
No		1,130	83.6		69,799	85.3	
Yes		222	16.4		12,068	14.7	
History of CVD							0.01
No		1,220	88.9		75,173	90.9	
Yes		153	11.1		7,622	9.2	
History of CHF							0.58
No		1,363	99.3		82,606	99.1	
Yes		10	0.7		724	0.9	
Warfarin use							0.58
No		1,355	98.7		82,376	98.9	
Yes		18	1.3		958	1.2	
Anti-arrhythmic use							0.48
No		1,369	99.7		82,989	99.6	
Yes		4	0.3		345	0.4	
Aspirin use							0.31
No		1,074	78.2		64,221	77.1	
Yes		299	21.8		19,113	22.9	
Statin use							0.83
No		1,264	92.1		76,589	91.9	
Yes		109	7.9		6,745	8.1	
β-blocker use							0.83
No		1,257	91.6		76,427	91.7	
Yes		116	8.5		6,908	8.3	
Calcium channel blocker use							0.33
No		1,230	89.6		75,306	90.4	
Yes		143	10.4		8,029	9.6	
ACE inhibitor use							0.98
No		1,265	92.1		76,794	92.2	
Yes		108	7.9		6,541	7.9	
Angiotensin II receptor blocker use							0.56
No		1,361	99.1		82,720	99.3	
Yes		12	0.9		615	0.7	

Table continues

Table 3. Continued

Characteristic	Incident Colorectal Cancer (n = 1,373)			No Incident Colorectal Cancer (n = 83,335)			*P* Value
	Mean (SD)	No.[a]	%	Mean (SD)	No.[a]	%	
Cardiac glycoside use							0.40
No		1,341	97.7		81,662	98.0	
Yes		32	2.3		1,672	2.0	

Abbreviations: ACE, angiotensin-converting enzyme; BMI, body mass index; CHF, congestive heart failure; CVD, cardiovascular disease; SD, standard deviation.
[a] Subgroup totals may not sum to the column total because of missing data.
[b] Weight (kg)/height (m)^2.

Table 4. Hazard Ratios for Incident Invasive Breast and Colorectal Cancer, by Self-Reported History of Atrial Fibrillation at Baseline, Women's Health Initiative, 1994–1998

Adjustment	Incident Invasive Breast Cancer (n = 65,352)[a]			Incident Colorectal Cancer (n = 76,252)[b]		
	HR	95% CI	*P* Value	HR	95% CI	*P* Value
None	1.23	1.06, 1.42	<0.01	1.17	0.91, 1.50	0.22
Age and race	1.19	1.03, 1.37	0.02	0.94	0.73, 1.21	0.66
Age, race, and potential confounders[c]	1.19	1.03, 1.38	0.02	0.91	0.71, 1.18	0.49
Variables above and cardiac glycoside use	1.01	0.85, 1.20	0.89	0.89	0.67, 1.19	0.43

Abbreviations: CI, confidence interval; HR, hazard ratio.
[a] There were 3,736 events over a median follow-up time of 15.3 years.
[b] There were 1,251 events over a median follow-up time of 15.9 years.
[c] In the invasive breast cancer model, potential confounders were those baseline characteristics that were associated with both atrial fibrillation prevalence and incident breast cancer: educational level, income, marital status, physical activity level, parity, age at menopause, hormone therapy use, hysterectomy, diabetes, and history of cardiovascular disease (myocardial infarction, stroke, transient ischemic attack, angina, or revascularization). In the colorectal cancer model, potential confounders were baseline characteristics that were associated with both atrial fibrillation prevalence and incident colorectal cancer: income, marital status, physical activity level, parity, hormone therapy use, hypertension, diabetes, resting pulse rate, and history of cardiovascular disease (myocardial infarction, stroke, transient ischemic attack, angina or revascularization).

Table 5. Adjusted[a] Hazard Ratios for Incident Invasive Breast Cancer, by Self-Reported Atrial Fibrillation and Glycoside Use at Baseline, Women's Health Initiative, 1994–1998

Mutually Exclusive Categories of Atrial Fibrillation and Cardiac Glycoside	Invasive Breast Cancer[b]					Colorectal Cancer[c]				
	Total Sample Size	No. of Events	HR	95% CI	*P* Value	Total Sample Size	No. Events	HR	95% CI	*P* Value
No atrial fibrillation, no cardiac glycosides	61,794	3,513	1.00	Referent		72,062	1,178	1.00	Referent	
Atrial fibrillation, no cardiac glycosides	2,281	121	1.01	0.85, 1.20	0.89	2,693	44	0.91	0.67, 1.23	0.54
Atrial fibrillation, cardiac glycosides	932	77	1.70	1.35, 2.13	<0.001	1,088	20	0.93	0.60, 1.46	0.76
No atrial fibrillation, cardiac glycosides	345	25	1.69	1.13, 2.50	0.01	409	9	1.18	0.61, 2.29	0.62

Abbreviations: CI, confidence interval; HR, hazard ratio.
[a] The invasive breast cancer model was adjusted for baseline characteristics that were associated with both atrial fibrillation prevalence and incident breast cancer: age, race, educational level, income, marital status, physical activity level, parity, age at menopause, hormone therapy use, hysterectomy, diabetes, and history of cardiovascular disease (myocardial infarction, stroke, transient ischemic attack, angina, or revascularization). The colorectal cancer model was adjusted for baseline characteristics that were associated with both atrial fibrillation prevalence and incident colorectal cancer: age, race, income, marital status, physical activity level, parity, hormone therapy use, hypertension, diabetes, resting pulse rate, and history of cardiovascular disease (myocardial infarction, stroke, transient ischemic attack, angina, or revascularization).
[b] The median follow-up time was 15.3 years.
[c] The median follow-up time was 15.9 years.

cardiac glycosides resulted in an attenuation of that risk, indicating that cardiac glycoside use is a partial mediator because cardiac glycosides may be prescribed for AF. However, it is also a confounder because not all AF is treated with glycosides. In our sample, 28% of those with AF at baseline were taking cardiac glycosides compared with 0.6% of those without AF. Thus, the excess risk of breast cancer observed with AF is explained by use of cardiac glycosides. The significant association of cardiac glycosides with incident breast cancer in our cohort is consistent with other research (13–15). However, it is also possible that other factors associated with use of cardiac glycosides result in a bias by indication.

Our results also differ from those from a study by Müller et al. (3) in which the authors showed a positive association of AF and atrial flutter with increased occurrence of colon cancer after 5–10 years. The authors examined discharge *International Classification of Diseases* codes to determine the frequency of individual diseases preceding colon cancer in the patient population. Although our sample population had a lower number of incident cases of colorectal cancer (n = 1,373) than did the population in the study by Müller et al. (n = 12,304), the latter study was a retrospective review of patient treatment files and discharge diagnoses. The authors indicated that although AF and atrial flutter did not represent any known risk factor, the usage of anticoagulants, such as warfarin or heparin, for the treatment of these arrhythmias may lead to chronic gastrointestinal bleeding and may be a possible mechanism for the association.

In conclusion, cardiac glycoside use was associated with a 68% higher risk of breast cancer. The association of risk of breast cancer with AF at baseline in postmenopausal women is explained by the use of cardiac glycosides. There was no association of AF with colorectal cancer incidence.

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