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Atrial Fibrillation in Breast Cancer Patients: Incidence, Prevalence, Risk Factors and Mortality: Longitudinal SEER-Medicare Analysis

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Degree to be awarded
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Atrial Fibrillation in Breast Cancer Patients: Incidence, Prevalence, Risk Factors and Mortality: Longitudinal SEER-Medicare Analysis

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Abstract

Background: The national incidence, risk factor, and associated mortality of atrial fibrillation (AF) in breast cancer patients are unknown.

Methods: Using the Surveillance, Epidemiology, and End Results–Medicare linked database, we identified females, ≥ 66-year-old, with a new primary diagnosis of breast cancer from 2007 through 2014. These patients were individually matched 1:1 to Medicare enrollees without cancer, and each pair was followed for one year to identify a primary outcome of AF. Cumulative incidence rates were calculated using competing risk survival statistics. Following this, identification of risk factors of AF among breast cancer patients was conducted using the adjusted Cox proportional hazards model. Finally, Kaplan-Meier methods and adjusted Cox proportional hazards modeling were performed to estimate mortality in breast cancer patients with incident and prevalent AF.

Results: This study included 85,423 breast cancer patients. Among these 9,425 (11.0%) had AF diagnosis prior to the breast cancer diagnosis. New AF was diagnosed in 2,993 (3.9%) patients in a 1-year period after the breast cancer diagnosis (incidence = 3.3% (95% CI = 3.0% - 3.5%) at 1-year; higher rate in the first 60 days (0.6%/month)]. Comparatively, the incidence of new AF in matched non-cancer controls was 1.8% (95% CI = 1.6% - 2.0%). Apart from traditional demographic and cardiovascular risk factors, breast cancer stage was strongly associated with development of AF [AJCC Stage 2 vs. 1: adjusted HR (aHR)= 1.51 (95% CI= 1.37 – 1.65); AJCC Stage 3 vs. 1: aHR= 2.63 (95% CI= 2.35 – 2.94); AJCC Stage 4 vs. 1: aHR= 4.21 (95% CI= 4.04 – 5.48)]. New onset AF after breast cancer diagnosis (aHR = 3.51 [95% CI = 1.69 – 7.32]) and prevalent AF prior to breast cancer diagnosis (aHR = 1.70 [95% CI = 1.26 – 2.29]) was associated with increased 1-year- cardiovascular mortality.

Conclusion: AF incidence is significantly higher in women after a breast cancer diagnosis. Apart from traditional risk factors, higher breast cancer stages at diagnosis are significantly associated with a higher risk of AF. New or prevalent AF in the setting of new breast cancer increases 1-year cardiovascular mortality but not breast cancer-related mortality.

Keywords: Atrial Fibrillation, breast cancer, incidence, risk factors, mortality, SEER-Medicare

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Chapter 1 Literature Review:

Full literature review

Atrial fibrillation (AF) is one of the most common forms of arrhythmias in the general population and is associated with significant thrombotic morbidities and overall cardiovascular mortality. [1] The prevalence of AF is expected to rise from ~ 5 million in 2010 to over 12 million by 2030 in the United States alone. [2] There has been a 5% annual increase in AF prevalence among Medicare beneficiaries (≥ 65 years) from 1993 to 2007 with a 2007 prevalence of 85.5 per 1000 beneficiaries. Prevalence was higher in the White race (90.8 per 1,000) than other races (46.3 per 1,000 in Black race, and 47.5 per 1,000 in other/unknown races). [3] This pattern of lower prevalence of AF in Blacks and Asians has been noted in the California state registry (odds ratio (OR), 0.49 [95% confidence interval (CI), 0.47–0.52]) for Black vs. White race; (OR, 0.68 [95% CI, 0.64–0.72]) for Asian vs. White race, respectively). [4] Similarly, the lifetime risk of AF in white females (30% [95% CI, 26%–32%]) is higher than Black females (21% [95% CI, 13%–24%]) as noted in the Atherosclerosis Risk in Community Study. [5]

AF occurrence is attributable to several risk factors, with the most substantial risk factor being age. [6] However, among population attributable risk factors, hypertension and obesity have the strongest association with AF occurrence. [7] Various other chronic disease conditions such as lung disease[8], chronic kidney disease[9], diabetes[10], and smoking[11] have been associated with AF. More recently, with the increased interest in cardio-oncology, there are growing reports that cancer and cancer medications are associated with an increased risk of AF.[12, 13]

AF is the most typical arrhythmia noted in cancer patients. [12] Cancer patients are about four times more likely to develop AF compared to the general population, as indicated by a study from the Danish national database (17.4 versus 3.7 per 1,000 person-years). [14] It was also noted

that the risk attributed to AF development declines with time since cancer diagnosis. [14] Over the years, there have been six significant studies that have tried to estimate the risk of AF in cancer patients that are listed in the **table** below:

First author and year	**Location**	**Period of enrollment**	**Study design**	**Total patients, *N***	**Cancer type**	**Incident cases of AF, *N* (%)**	**Follow-up (year)**
Guzzetti 2008[15]	Italy	1987–2004	Case-control	1,868	Colorectal and breast cancer	49 (2.6)	NA
Jakobsen 2015[14]	Denmark	2000–2012	Prospective cohort	5,539,824	All types of cancer	NA	12
Nouraie 2015[16]	USA	2000–2012	Retrospective cohort	1,258	Colorectal cancer	93 (7.4)	NA
Conen 2016[17]	USA	1993–2013	Prospective cohort	34,691	All types of cancer	824 (2.3)	19.1
D'Souza 2019[18]	Denmark	1998-2015	Prospective cohort	74,155	Breast cancer	987 (1.33)	3
Abdel-Qadir 2019[19]	Canada	2007-2016	Retrospective cohort	68,113	Breast cancer	3,131 (4.6)	9

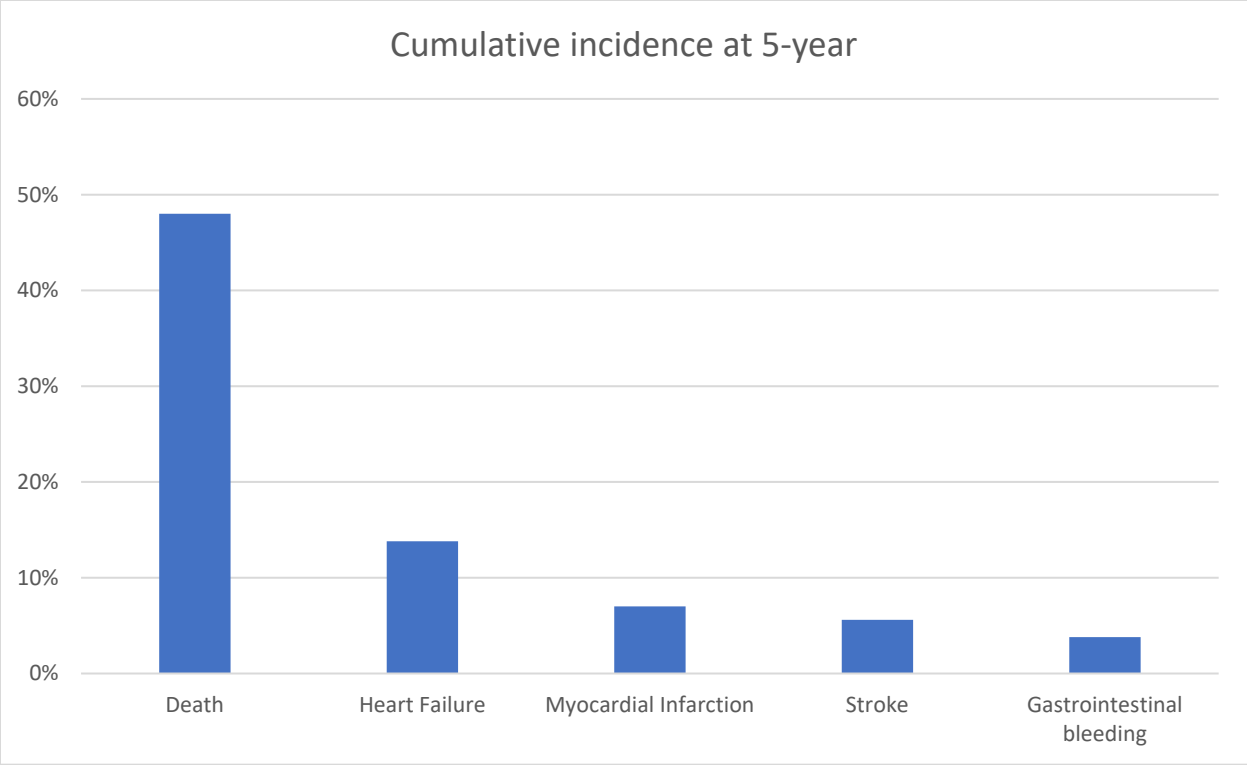
The prevalence of AF has been projected to be ~15-30% in those with cancer. [12] AF is thought to be a marker of occult cancer, i.e., there is an increase in AF diagnosis around the time of cancer diagnosis. [20, 21] This is likely due to a shared risk factor between cancer and cardiovascular disease and mechanistically a result of increased inflammatory milieu. [22] In fact, reversal of inflammation as seen in the Canakinumab Anti-inflammatory Thrombosis Outcomes

Study (CANTOS) trial where anti-interleukin 1β, Canakinumab, showed a reduction of cardiovascular disease[23] also showed an overall lower incidence of lung cancer in a 2-year follow-up. [24] However, data regarding AF prevalence and incidence in a multi-ethnic representative cohort of American patients with breast cancer has not been presented to date.

The risk of AF has been associated with various traditional cardiovascular risk factors, as discussed above. However, the study by Abdel-Qadir et al.[19] highlighted the importance of cancer stage, grade, therapy as potential risk factors for AF. As expected, cardiovascular risk factors such as heart failure (HR = 1.29 [95% CI: 1.08-1.53]) and diabetes (HR = 1.15 [95% CI: 1.04-1.28]) were associated with AF development after breast cancer diagnosis. Interestingly, stage of cancer, laterality of breast cancer, and mastectomy as treatment for breast cancer were not significantly associated with AF after a breast cancer diagnosis. Although there was increased likelihood of AF after chemotherapy exposure (HR = 1.23 [95% CI: 1.13-1.35]), anthracycline exposure (HR = 1.12 [95% CI: 0.92-1.38]) and trastuzumab (HR = 0.98 [95% CI: 0.74-1.30]) exposure were not individually associated with AF after breast cancer diagnosis.

It is evident that AF leads to an overall poorer prognosis after diagnosis. [25] The age-adjusted mortality rate attributable to AF is 6.4 per 100,000 people in 2018. [1] An adjusted analysis from the Framingham study showed an increase in AF-related mortality in females (OR, 1.9 [95% CI, 1.5–2.2]) compared to males (OR, 1.5 [95% CI, 1.2–1.8]), which was also confirmed in a meta-analysis. [26, 27] In a study of the Medicare population (age > 65 years)[25], once diagnosed with AF, patients have various events attributed to AF (see **figure**).

Figure: 5-year cumulative incidence of various events at a 5-year period after diagnosis of AF in a Medicare population. Adapted from Piccini JP et al.[25]



However, mortality was the commonest event at five years with a cumulative incidence of 19.5% at 1 year and 48.8% at 5 years. [25] There is no significant data regarding the outcomes of AF after cancer diagnosis and how it affects cancer prognosis.

Statement of the problem

The burden of AF in a multi-ethnic representative cohort of breast cancer patients has not been established. The effects of traditional, and potential cancer-specific risk factors, needs to be further evaluated in a contemporary breast cancer cohort. Finally, the effect of incident AF on mortality outcomes among breast cancer patients remains to be determined.

Purpose of the thesis

In this manuscript, we use the Surveillance, Epidemiology, and End Results Program (SEER) and Medicare-merged dataset, which is a nationally representative dataset of the US

Cancer population, to estimate the incidence and risk factors for developments of AF in females with breast cancer. Additionally, we also quantified the impact of AF on all-cause, cancer-related, and cardiovascular mortality among females with breast cancer.

Chapter 2 Journal Article

Introduction

Atrial fibrillation (AF) is one of the most common forms of arrhythmias in the general population and is associated with significant thrombotic morbidity and overall cardiovascular mortality.[1] AF occurrence is attributable to several risk factors such as hypertension and obesity.[6-11] The prevalence of AF is expected to rise from ~ 5 million in 2010 to over 12 million by 2030 in the United States alone.[2-4] The lifetime risk of AF is reportedly higher in white females [30% (95% CI, 26%–32%)] compared with black females [21% (95% CI, 13%–24%)] as noted in the Atherosclerosis Risk in Community Study.[5]

AF is one of the most typical arrhythmias noted in cancer patients.[12] Cancer patients are about four times more likely to develop AF compared to the general population.[14-19, 28] The association between AF and cancer is likely due in part to shared risk factors between the two diseases and mechanistically may be linked to the increased inflammatory milieu. [22] Recent studies suggest that cancer medications are associated with an increased risk of AF.[12, 13] A study by Abdel-Qadir et al.[19] also indicates that cancer stage is a potential risk factor for AF.

It is evident that AF is associated with an overall poor prognosis after diagnosis.[25-27] In a Medicare population, mortality was the commonest event at five years, with a cumulative incidence of 19.5% at 1 year and 48.8% at 5 years.[25] Little is known regarding the outcomes of AF after a cancer diagnosis or how AF affects cancer prognosis. Moreover, the burden of AF in a multi-ethnic representative cohort of breast cancer patients has not been established. The effects of traditional and potential cancer-specific risk factors on AF development in a contemporary breast cancer cohort need to be established. Finally, the impact of incident AF on mortality outcomes among breast cancer patients remains to be determined.

Methods

Data Source

This study used the SEER-Medicare linked databases from the year 2007 to 2014. [29] The SEER program, supported by the National Cancer Institute (NCI), collects data from various state registries and covers 35% of the US population. The Medicare program insures over 95% of Americans above the age of 65 years. The SEER-Medicare linkage started in 1991 and has been updated every 3-4 years, with the final relevant linkage done in 2014. [29] For each linkage, 95% of persons aged 65 and older in SEER files were matched to the Medicare enrollment files. SEER also provides data from a 5% random sample of Medicare beneficiaries without cancer residing in SEER geographic regions, which enabled us to compare the risk of AF in patients with breast cancer versus matched patients without cancer. The Ohio State University's institutional review board approved this study under exempt status due to the deidentified nature of the registry. The date of the last follow-up was December 31, 2014.

Study Population

This study included females who were 66 years old or older when they were diagnosed with breast cancer between 2007 and 2013. Breast cancer was identified using the ICD-O-3 site recode classification C500 to C509. This study required the patients to have Medicare Parts A and B and not be members of a health maintenance organization (HMO) for one year before and after their breast cancer diagnosis to identify comorbidities and AF because Medicare claims are not complete for HMO members. Additionally, the patient should have qualified for Medicare due to age only. Patients were also excluded if their cancer was diagnosed at autopsy, their month of cancer diagnosis was missing, if the patient was at a pre-cancerous or in-situ stage at diagnosis, or had any other form of cancer ever. [30]

The non-cancer control population[31, 32] was found in the 5% sample of non-cancer patients who were matched by year of birth, gender, race (white or nonwhite [Black, Asian, Pacific Islander, other]), SEER registry (a surrogate for geographic region categorized into Northeast, South, Midwest, and West regions), and Charlson comorbidity index in the year before study entry (dichotomized into 0 or ≥1). The index date for matching was also referred to as pseudo-diagnosis date in the non-cancer controls. Control patients without cancer were ineligible for matching if they lacked Medicare Part A or B coverage, belonged to an HMO as above, or had a Medicare claim for AF before the index date. The non-cancer patients were first matched using incidence-density sampling, where one breast cancer patient was matched to multiple non-cancer patients. Then the control group was narrowed to a 1:1 match using a propensity-matched sample using caliper matching where caliper width was set at 10%.

Data Extraction and Definitions

Administrative codes are a reliable method to identify cardiac conditions with a high level of positive predictive value. We used two different ways to find a new and prior diagnosis of AF. The cohort of breast cancer patients and matched non-cancer patients were merged to their Medicare inpatient, outpatient, and provider claims. These claims were coded using ICD-9CM codes. Those who had at least one inpatient, one provider, or two outpatient claims for AF (427.31) after breast cancer diagnosis were considered to have new-onset AF.[33] The chronic condition flag file that accompanies the claims file and is a part of the Chronic Condition segment of the Master Beneficiary Summary File was also utilized to identify AF since it is one of the 27 tracked chronic conditions. If the AF diagnosis date appeared in more than one source, then the earliest date of diagnosis was used. Those who were determined to have AF before cancer diagnosis were considered to have a prior diagnosis of AF.

Covariates were divided into three broad groups, namely, demographic, cancer-specific, and non-cancer comorbidities. Demographic covariates included age at cancer diagnosis, race, Hispanic ethnicity, SEER registry, marital status, urban location of residence, and poverty classification based on the nationwide scale. Cancer-specific details include cancer laterality, North American Association of Central Cancer Registries (NAACCR) grade, American Joint Committee on Cancer (AJCC) stage, SEER stage, surgical therapy, lymph node biopsy status, radiation therapy, estrogen-receptor-status, progesterone-receptor-status, and human epidermal growth factor receptor 2 (HER2)-status. Further cancer covariates included the use of infusion-based anti-cancer therapy and the length of this therapy. These included anthracyclines, Her2-targeted therapies, cyclophosphamide, taxanes, and platinum-based agents. [34] Among those who participated in Medicare Part-D from cancer diagnosis until two years after or 2014, whichever was sooner, oral anti-cancer medication details were obtained. Specifically, medication use status and length of therapy were obtained for those who were prescribed hormonal therapy and oral Her2-targeted therapies. [35] The detailed methodology of the definition of each covariate and the source of data are listed in **Supplemental Table 1**. A comorbidity score was calculated using the cancer-specific SEER-Medicare comorbidity index and Klabunde's adaptation of the Charlson comorbidity index. [36]

Outcomes

This study quantifies the incidence of AF in those with a new diagnosis of breast cancer compared to those without cancer, identifies the cancer-specific risk factors that contribute to the incidence of AF, and assesses if prevalent or incident AF contributes to increased mortality after the breast cancer diagnosis. Secondary outcomes include quantification of cause-specific mortality.

Statistical analysis

Descriptive statistics were used to evaluate baseline characteristics of breast cancer patients stratified by the development of AF. As death is a frequent competing risk in patients with cancer and can prevent AF events from being observed, competing risk survival statistics accounting for death were used to calculate the cumulative incidence of AF. [37] Prior studies have shown that following cancer patients for a long-time lead to proportional hazards assumption violation, perhaps due to differential mortality in different cancer strata; hence we limited the incidence and hazard ratio quantification to 1-year. [38] The incidence of AF incidence between breast cancer and non-cancer patients was compared by performing the Gray-K test. Follow-up was calculated from the case patient's date of cancer diagnosis until AF (event), death (competing risk), or end of study (end of follow up). We further presented the standardized incidence rates as 1-year in comparison to the Piccini et al. article.[39]

To evaluate the association of cancer-specific variables with the development of new-onset AF, all covariates were checked for proportional hazards assumption. Schoenfeld's residual P-values and univariable hazard ratios from Cox models for all variables are presented in supplemental Table 1. If cancer-specific variables did not meet the proportional hazards assumption, then extended Cox models were used. The non-cancer variables that met proportional hazards assumption were used for adjusting in a Fine-Gray competing risk model where cause-specific hazards ratios were presented for cancer-specific risk factors. The non-cancer variables that did not meet the proportional hazards assumption were added as stratifying variables. The final multivariable model was adjusted or stratified for age, race, Hispanic ethnicity, SEER-registry, marital status, urban location of the patient, poverty level, marital status, history of obesity, history of smoking, history of hypertension, history of stroke, and

SEER-Medicare comorbidity index. The decision to not include variables in the final model was based on the univariable hazard ratio results or if the variable was accounted for by the SEER-Medicare index, thus avoiding multicollinearity. An interaction term was introduced in the model to study one significant cancer-specific variable's effect in relation to another significant cancer-specific variable. This is also known as a joint test. [40] For example, if radiation therapy is significant in the above analysis, effect modification of breast cancer surgery and cancer stage were evaluated in the subgroup of patients who underwent radiation therapy and in those who didn't. Missing data were not imputed due to sufficient statistical power obtained from patients where data were available. However, none of the cancer variables analyzed had >10% missingness.

After appropriate proportional hazards testing, proportions, 1-year overall survival rates, and hazard ratios (HRs) for all-cause mortality stratified by the incident and prevalent AF were calculated. Unadjusted Kaplan–Meier survival curves were generated to determine median-time-to event for mortality in those who developed AF. Multivariable Cox proportional hazards models were used to estimate the association between AF and all-cause mortality in the form of crude and adjusted HRs. The adjustment scheme included variables in the following order: demographics, followed by breast cancer-specific variables, followed by cardiovascular comorbidities, and finally, anti-cancer medications (**supplemental table 2**). This analysis was repeated for cancer-specific, determined by breast cancer cause of death code of 26000, and cardiovascular-mortality, determined by death code for "disease of heart" (50060) or "cerebrovascular diseases" (50080). Those breast cancer patients who died of other etiologies contributed person-time to the analysis until the end of follow-up due to mortality from a

different cause than being assessed. Using the unadjusted (model 1, **supplemental table 2**) and fully adjusted model (model 6, **supplemental table 2**), Kaplan-Meier curves were generated.

SAS version 9.4 (Cary, NC) was used for analysis. All statistical tests were two-sided, and a P value less than 0.05 was considered statistically significant.

Results

Demographics

There were 85,423 breast cancer patients above the age of 66 who were included in this study (**figure 1**). Among these 9,425 (11.0%) had AF diagnosis prior to the breast cancer diagnosis. There were 2,993 (3.9%) new AF diagnosed in a 1-year period after the breast cancer diagnosis. The characteristics of breast cancer patients with a new diagnosis of AF, prevalent AF, and no AF diagnosis at 1-year are presented in **table 1**. We observe that those with new or prevalent AF were older ($P < 0.001$). Additionally, we note that AF incidence after breast cancer diagnosis was higher in those who did not receive surgery (23.5% vs. 10.4%; $P < 0.001$) or radiation (66.5% vs. 52.3%; $P < 0.001$) as their first course of therapy and were at a higher AJCC stage at diagnosis (stage IV 14.8% vs. 6.3%; $P < 0.001$).

Incidence

The incidence of new-onset AF after breast cancer diagnosis is 0.6% [95% confidence interval (CI) = 0.5% – 0.7%] at 30 days, 2.1% [95% CI = 1.9% - 2.4%] at 6-months and 3.3% [95% CI = 3.0% - 3.5%] at 1-year respectively. This remained higher than the non-cancer matched control (**figure 2**). Among the breast cancer population itself (N = 75,998), the rate of AF diagnosis is highest in the first 60 days, increasing at a rate of 0.6%/30-days and slows after that to increase at the rate of 0.3%/30-days over the period of 1-year of follow up (**supplemental figure 1A**). The 1-year incidence across the entire cohort is 40.4 per 1000 person-years

(**supplemental figure 1B**). The race-standardized AF incidence is 31.9 per 1000 person-years in females age 66-70 years, with an increase in AF incidence with age. From 2007 to 2014, there has been an annual increase of AF incidence by 3.4% (**supplemental table 3**). The age-standardized AF incidence was 49.9 per 1000 person-years in whites vs. 58.8 per 1000 person-years in Black females in 2014.

Risk Factors for AF

Age, race, and several other socioeconomic features were strongly associated with development of new onset AF in females with breast cancer (**supplemental table 1**). Multiple cardiovascular risk factors such as hypertension (HR = 1.46 [95% CI = 1.34 – 1.58]), diabetes (HR= 1.55 [95% CI= 1.44 – 1.67]), prior history of stroke (HR= 1.70 [95% CI= 1.53 – 1.88]), and the NCI comorbidity index above 0 (HR= 1.84 [95% CI= 1.70 – 2.00]) were associated with new diagnosis of AF. Notably, a history of depression (HR= 1.21 [95% CI= 1.12 – 1.32]), and anemia (HR= 1.46 [95% CI= 1.36 – 1.57]) were also associated with development of AF. Among the cancer specific covariates, cancer stage was strongly associated with development of AF (AJCC Stage 2 vs. 1: adjusted HR (aHR)= 1.51 [95% CI= 1.37 – 1.65]; AJCC Stage 3 vs. 1: aHR= 2.63 [95% CI= 2.35 – 2.94]; AJCC Stage 4 vs. 1: aHR= 4.21 [95% CI= 4.04 – 5.48]). Surgery and radiation therapy as first option for breast cancer treatment after diagnosis was associated with reduced risk of AF (**table 2**; aHR of modified radical mastectomy vs. no surgery as first treatment option = 0.46 [95% CI= 0.38 – 0.53]; aHR of beam radiation vs. no radiation therapy as first option = 0.66 [95% CI= 0.61 – 0.72]).

There was no difference in risk for AF by other cancer variables except those receiving Her2-targeted therapies as the first line of therapy after breast cancer diagnosis in those with grade 3 breast cancer (aHR = 0.44; 95% CI = 0.32 – 0.60; joint test P-value across all grades =

0.008; **supplemental table 4**). A difference was noted across the various AJCC stages when the joint test P-value was considered across the four AJCC cancer stages (**supplemental table 5**). HER-/HR+ receptor status was associated with a lower risk of AF in those with stage 1 (aHR = 0.71; 95% CI = 0.52 – 0.97) and stage 2 (aHR = 0.75; 95% CI = 0.57 – 0.99) disease as compared to those with HER+/HR+ receptor status. The various subgroups of the first choice of treatment among the surgical options and radiotherapy are presented in **supplemental tables 6** and **7,** respectively. There was no difference across the various cancer variables when risk factors for AF were assessed based on receptor status (Her2Neu and HR; **supplemental table 8**).

Mortality

Mortality differed among breast cancer patients depending on the time of AF development. We studied 2 groups: those who developed AF within 30-days after breast cancer diagnosis (group 1), and those who had prevalent AF prior to breast cancer diagnosis (group 2). Among those who developed AF within the first 30-days of breast cancer diagnosis (group 1), the 1-year survival was 62.2% (95% CI = 57.6% – 67.1%, **supplemental figure 2A**). However, 1 – year survival among those in group 2 was ~85% (**supplemental figure 2B**). In the adjusted Cox proportional hazards model, after full adjustment (model 6, **table 3**), there is significant increase in all-cause mortality at 1 year with incident AF within the first 30-days of breast cancer diagnosis (group 1; aHR = 2.05 [95% CI = 1.36 – 3.10]; **figure 3A and B**) but no difference in those with prevalent AF (group 2; aHR = 1.16 [95% CI = 0.99 – 1.36]; **supplemental figure 3A and B**). There is increased cardiovascular mortality in breast cancer patients with incident AF within the first 30-days of breast cancer diagnosis (table 3 model 6, group 1: aHR = 3.51 [95% CI = 1.69 – 7.32]; **figure 4 A and B**) and in those with prevalent AF (table 3 model 6, group 2: aHR = 1.70 [95% CI = 1.26 – 2.29]; **figure 4 C and D**). There is no difference breast cancer-

specific mortality at 1-year either in females with breast cancer and new AF within 30-days of breast cancer diagnosis (table 3 model 6, group 1: aHR = 1.74 [95% CI = 0.94 – 3.21]; **supplemental figure 4 A and B**), or in those with prevalent AF (table 3 model 6, group 2: aHR = 0.88 [95% CI = 0.68 – 1.14]; **supplemental figure 5 A and B**).

Discussion

In this contemporary evaluation of older female breast cancer patients, the incidence, risk factor, and mortality associated with AF were quantified using the SEER-Medicare registry. The incidence rate was higher in the first 60 days, and highest among older and Black females. Breast cancer severity, i.e., stage and grade, is strongly associated with the risk of AF development. Notably, patients undergoing surgical therapy, radiation therapy, and hormonal therapy as the first choice of breast cancer treatment were at a lower risk of developing AF. Breast cancer patients with prevalent AF prior to breast cancer diagnosis or new-onset AF within the first month after breast cancer diagnosis have lower survival than those without AF. In fully adjusted models, mortality in breast cancer patients is higher at 1-year among those who have new-onset AF after a breast cancer diagnosis, and this mortality risk is predominantly cardiovascular and not related to breast cancer. Involvement of cardiovascular specialists or cardio-oncology programs in the care of breast cancer patients who develop AF after diagnosis of cancer should be encouraged.

This study presents the incidence of AF after breast cancer diagnosis in a multi-ethnic and nationally representative cohort of breast cancer patients. The incidence of AF is known to be higher in whites compared to Black individuals. [3, 4] Here, we find an opposite trend. Although not wholly explained by our data, Black females have a higher likelihood of ER/PR- and later stage of a breast cancer diagnosis, which may be contributing factors. [41, 42] Our finding

that patients who take hormonal therapy are at a relatively lower risk of AF may also help to explain the higher incidence of AF in Black females. Additionally, we found that the incidence of AF is higher in the first 60 days after a cancer diagnosis. This finding is in line with that of Abdel-Qadir et al. and Mathews et al.,[19, 28] who observed a higher rate of AF in the first year after a breast cancer diagnosis, and contradictory to that of D'Souza et al., where the AF rate was lower in the first six months after a breast cancer diagnosis compared with matched controls in those above the age of 60.[18] It is important to note that the D'Souza et al. study was conducted in Denmark and hence does not reflect our study's multi-ethnic composition. Nevertheless, they observed that the risk of AF increased after the 1st six months in patients with breast cancer compared to non-cancer controls, similar to our study. Although no direct evidence was provided in that study, it was speculated that the increased incidence of AF subsequent to cancer diagnosis might be biologically explained by pro-inflammatory state, electrolyte and fluid imbalance, as well as a direct effect of cancer therapy.[22] It may also be epidemiologically explained by lead-time bias due to a higher level of comprehensive screening for various cardiovascular comorbidities that may affect cancer therapy.[43] Finally, Navi et al. noted an increase in stroke risk in the first year after cancer diagnosis in another SEER-Medicare analysis.[44] This increase in stroke risk may now be partially explained by the increase in AF burden after a cancer diagnosis, as noted in our study.

Higher breast cancer stage and grade stood out as significant risk factors associated with AF incidence. Remarkably, left-sided breast cancer and breast cancer subtype based on receptor status (Her2Neu/HR) were not associated with AF risk. Moreover, initial treatment with surgery, radiation, or hormonal therapy was noted to be associated with a lower risk of AF development. Furthermore, neither anthracycline nor Her2-targeted therapy was found to increase the risk of

AF, consistent with the findings of Abdel-Qadir et al. [19] In contrast to Abdel-Qadir et al., however, we found a strong positive association of AF with the cancer stage. [19] Taken together, it seems that AF development after a breast cancer diagnosis likely emanates from poor systemic health related to the cancer state rather than cardiotoxic therapies.

This was the first study to evaluate AF's role concerning mortality after a breast cancer diagnosis. It is noted that new-onset AF worsens all-cause mortality, which is mainly driven by cardiovascular mortality. There is no change in breast cancer-related mortality in those with new or prevalent AF. The increased mortality is similar to that observed in patients with left ventricular dysfunction after cancer diagnosis due to cancer therapy or other causes.[45, 46] The data regarding left ventricular dysfunction and heart failure after a cancer diagnosis have spurred the field of cardio-oncology since closely monitoring patients by specialists in cardio-oncology tends to result in a better outcome.[47] This study adds further to the evidence that is screening patients in the first month after the cancer diagnosis, and managing AF appropriately, may help to reduce morbidity and mortality. Given that AF was not associated with any specific cancer therapy, this study is reassuring from the standpoint of continuing cancer therapy even after AF diagnosis.

Limitations

Several limitations must be addressed in this study. First, patients below the age of 66 were excluded since we could only study enrollees in Medicare. Second, given that this study is based on medical claims, the findings are potentially less reliable than clinically collected data. Nevertheless, prior studies have shown good sensitivity and specificity of AF diagnosis in Medicare claims.[48] Additionally, the increased likelihood of cardiovascular events proximal to a cancer diagnosis has been noted in other SEER-Medicare studies. [44] Third, even though we

performed two-step matching for cancer and non-cancer patients using incidence density sampling followed by propensity matching, it is likely that there were hidden confounders that could not be accounted for. Such confounders may explain our observations that AF increases dramatically after cancer diagnosis and then decreases over time, which is biologically implausible. This issue may be resolvable by future studies on this topic. Fourth, SEER-Medicare covers ~30% of the United States[29] and represents the population at large; nevertheless, and minor discrepancies may be seen if we could gather data from the entire United States. Fifth, even though Medicare claims may identify major conditions like AF, the prevalence of obesity was noted to be around 3-10% in our study. This finding likely represents obesity ICD-9 code under-reporting, given that at least one-third of Americans above the age of 65 are obese. [49] Finally, this study was conducted in the period of 2007 to 2014. This was partly because of a change in claims from ICD-9 to ICD-10 in 2015 that would likely have increased the amount of error without necessarily changing the results.

Conclusion

AF incidence is significantly higher in women after a breast cancer diagnosis, particularly in black women. Apart from traditional risk factors, higher breast cancer stages and grades at diagnosis are associated with increased risk of AF, suggesting a systemic effect of advanced breast cancer itself on the heart. This illustrates the importance of guideline-directed screening for breast cancer, which would likely lead to the identification of more patients with early-stage breast cancer, which in turn may reduce the development of AF and its downstream effects. All-cause mortality was found to be increased in those with breast cancer who have new-onset AF, which is mainly driven by cardiovascular mortality and not breast cancer-related mortality.

Reducing the risk of AF development by reducing several modifiable risk factors would likely improve survival outcomes after breast cancer.

Chapter 3

Conclusions:

In summary, AF incidence is significantly higher in women after a breast cancer diagnosis, particularly in Black women. Apart from traditional risk factors, higher breast cancer stages and grades at diagnosis are significantly associated with a higher risk of AF. All-cause mortality is increased in those with breast cancer who have new-onset AF, and it is mainly driven by cardiovascular mortality and not breast cancer-related mortality.

Future directions:

The first step is to confirm the findings in another multi-ethnic registry prospectively. Given that several risk factors, especially cardiovascular, are modifiable, special efforts by referring cancer patients to onco-primary care, cardio-oncology, and preventive cardiology would help prevent AF occurrence. There are other aspects of AF development that need to be studied as well. These include stroke or other embolic complications after AF in cancer and how the natural history differs from non-cancer patients. AF management algorithms are different in the first year of a cancer diagnosis. There is a greater emphasis on rate control and lower anticoagulation use due to the risk of bleeding. [12, 50] Whether this disparity is warranted or merely a gestalt based on intuition needs to be studied. This would include systematically studying the use of anti-arrhythmic drugs, cardiac ablation, and the use of left atrial occluder devices. [51]

Public health implications:

There are several public health implications of this research. The burden of breast cancer has been on the rise. There have been significant developments in oncology that have led to improved survival after the diagnosis of cancer. In 2021, a patient diagnosed with breast cancer

is expected to have over 90% 5-year survival. [52] This study shows that patients with breast cancer diagnosis are at a higher risk of AF, affecting their overall survival at one year. Thus, reducing the risk of AF development by reducing several modifiable risk factors that we found in this study would improve survival outcomes after breast cancer. This study is also indicative of the importance of screening for breast cancer. Since we found a closer association of breast cancer stage at diagnosis with development of AF, standard guideline-directed mammography and self/clinical breast exam screening would likely discover more patients with early-stage breast cancer, thus reducing the likelihood of AF and its downstream effect.

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Table 1: Characteristics of breast cancer patients included in the study by AF status, Medicare 2007 to 2014.

Variable	New Atrial Fibrillation after Cancer Diagnosis (N = 2,993)	Prior Atrial Fibrillation before Cancer Diagnosis (N = 9,425)	No Atrial Fibrillation in 1-year follow-up (N = (73,005)	P-value*
Age at cancer diagnosis (Median [Interquartile range])	78 (72 – 84)	81 (75 – 85)	74 (69 – 80)	<0.001
Race (N, %)				<0.001
White	2,585 (86.4)	8,590 (91.1)	61,879 (84.8)	
Black	280 (9.4)	571 (6.1)	6,686 (9.2)	
Other	128 (4.3)	264 (2.8)	4,440 (6.1)	
Hispanic (N, %)	144 (4.8)	377 (4.0)	4,721 (6.5)	<0.001
Registry (N, %)[†]				<0.001
West	1,227 (41.0)	3,579 (38.0)	31,642 (43.3)	
Northeast	649 (21.7)	2,074 (22.0)	13,423 (18.4)	
Midwest	544 (18.2)	1,837 (19.5)	12,495 (17.1)	
South	573 (19.1)	1,935 (20.5)	15,445 (21.2)	
Marital Status (N, %)				<0.001
Unmarried-Single	271 (9.1)	651 (6.9)	6,440 (8.8)	
Married	1,089 (36.4)	3,192 (33.9)	32,237 (44.2)	
Previously Married	1,499 (50.1)	5,205 (55.2)	31,226 (42.8)	
Unmarried partnered	134 (4.5)	377 (4.0)	3,102 (4.3)	
Urban (N, %)				0.0002
Large metro	1,783 (59.6)	5,178 (54.9)	40,684 (55.8)	
Small metro	805 (26.9)	2,788 (29.6)	21,768 (29.8)	
Other Urban areas	362 (12.1)	1,285 (13.6)	9,285 (12.7)	
Rural	43 (1.4)	174 (1.9)	1,268 (1.7)	
Poverty (N, %)				0.47
0% - < 5%	678 (23.0)	2,228 (24.0)	17,478 (24.2)	
5 - <10%	837 (28.4)	2,594 (27.9)	19,793 (27.4)	
10 - <20%	861 (29.2)	2,705 (29.1)	20,758 (28.8)	
20 – 100%	572 (19.4)	1,762 (19.0)	14,135 (19.6)	
Breast Cancer Characteristics[?]				
Laterality – left (N, %)	1,482 (50.2)	4,742 (50.8)	37,219 (51.3)	0.32
Grade (N, %)				<0.001
1	481 (18.4)	2,169 (25.6)	17,595 (26.1)	
2	1,161 (44.4)	3,839 (45.2)	31,217 (46.4)	
3	958 (36.6)	2,418 (28.5)	18,188 (27.0)	
4	15 (0.6)	59 (0.7)	343 (0.5)	
AJCC stage (N, %)[‡]				<0.001
I	987 (35.5)	4,205 (48.5)	37,182 (53.3)	

II	908 (32.6)	2,947 (34.0)	21,630 (31.0)	
III	476 (17.1)	945 (10.9)	6,509 (9.3)	
IV	411 (14.8)	568 (6.6)	4,384 (6.3)	
SEER stage (N, %)				<0.001
I (localized)	1,540 (52.5)	6,125 (66.7)	49,692 (69.0)	
II (regional direct extension)	157 (5.4)	438 (4.8)	2,062 (2.9)	
III (regional lymph node extension only)	599 (20.4)	1,627 (17.7)	13,206 (18.3)	
IV (regional direct and lymph node extension)	218 (7.4)	410 (4.5)	2,624 (3.6)	
VII (distant)	417 (14.2)	587 (6.4)	4,478 (6.2)	
Surgical therapy (N, %)				<0.001
No surgery	682 (23.5)	1,573 (17.0)	7,277 (10.4)	
Localized therapy such as lumpectomy	1,217 (41.9)	4,618 (50.0)	40,754 (58.0)	
Total simple mastectomy	452 (15.6)	1,495 (16.2)	11,173 (15.9)	
Modified radical mastectomy	556 (19.1)	1,557 (16.9)	11,038 (15.7)	
Lymph node surgery (N, %)				<0.001
Less than 4 lymph nodes removed	938 (48.1)	3,460 (55.7)	34,829 (59.1)	
Greater than equal to 4 lymph nodes removed	1,013 (51.9)	2,756 (44.3)	24,080 (40.9)	
Radiation therapy (N, %)				<0.001
No radiotherapy	1,869 (66.5)	5,908 (66.7)	35,885 (52.3)	
Beam radiation	902 (32.1)	2,731 (30.8)	30,155 (43.9)	
Implanted radiation	40 (1.4)	220 (2.5)	2,631 (3.8)	
Tumor Estrogen Receptor Status (N, %)	2,191 (80.3)	7,434 (85.0)	59,082 (85.4)	<0.001
Tumor Progesterone Receptor Status (N, %)	1,816 (67.0)	6,324 (72.8)	50,440 (73.4)	<0.001
Tumor human epidermal growth factor receptor (HER) 2 Status (N, %)[§]	237 (14.0)	563 (11.3)	4,323 (10.9)	0.0003
Breast tumor subtype based on combination receptor status (N, %)[§]				<0.001
HER2+/hormone receptor (HR)+	158 (9.4)	400 (8.1)	2,985 (7.5)	
HER2+/HR-	77 (4.6)	161 (3.2)	1,325 (3.4)	
HER2-/HR+	1,233 (73.4)	3,905 (78.7)	31,451 (79.5)	
HER2-/HR-	213 (12.7)	496 (10.0)	3,809 (9.6)	
Comorbidities before breast cancer diagnosis (N, %)				

Hypertension	22,234 (74.6)	8,874 (94.2)	48,725 (66.7)	<0.001
Diabetes	1,115 (37.3)	4,295 (45.6)	20,155 (27.6)	<0.001
Obesity^	233 (7.8)	981 (10.4)	2,281 (3.1)	<0.001
History of ischemic stroke/Transient ischemic attack	429 (14.3)	2,509 (26.6)	6,552 (9.0)	<0.001
Hyperlipidemia	1,933 (64.6)	7,944 (84.3)	46,117 (63.2)	<0.001
History of congestive heart failure	935 (31.2)	5,824 (61.8)	11,487 (15.7)	<0.001
History of myocardial infarction	121 (4.0)	726 (7.7)	1,310 (1.8)	<0.001
History of ischemic heart disease	1,340 (44.8)	7,158 (76.0)	23,205 (31.8)	<0.001
History of lung disease	714 (23.9)	3,451 (36.6)	11,852 (16.2)	<0.001
Smoking^	377 (12.6)	1,388 (14.7)	4,616 (6.3)	<0.001
Peripheral vascular disease	208 (7.0)	1,090 (11.6)	2,732 (3.7)	<0.001
Rheumatological diseases	1,506 (50.3)	6,526 (69.2)	32,984 (45.2)	<0.001
Alzheimer's dementia	393 (13.1)	1,842 (19.5)	5,982 (8.2)	<0.001
History of depression	749 (25.0)	3,356 (35.6)	15,818 (21.7)	<0.001
Chronic kidney disease	545 (18.2)	2,722 (28.9)	7,909 (10.8)	<0.001
History of anemia	1,492 (49.9)	6,629 (70.3)	29,557 (40.5)	<0.001
History of Hypothyroidism	780 (26.1)	3,888 (41.3)	17,764 (24.3)	<0.001
Charlson's comorbidity index** (mean ± SD)	0.71±1.60	1.18±2.05	0.36±1.03	<0.001
National Cancer Institute comorbidity index**	0.76±1.51	1.28±1.90	0.43±1.04	<0.001

* P – value is Pearson's ChiSq test for categorical variables and ANOVA for continuous variables.

† West = San Francisco, Hawaii, New Mexico, Seattle, Utah, San Jose, Los Angeles; Northeast = Connecticut, New Jersey; Midwest = Detroit, Iowa, Kentucky; South = Atlanta, rural Georgia, Louisiana, greater Georgia

? present proportions exclude missing data.

‡ II (includes II, II not otherwise specified, IIA, IIB, IIC); III (includes III, III not otherwise specified, IIIA, IIIB, IIIC); IV (includes IV, IV not otherwise specified, IVA, IVB, IVC)

§ Only available after 2010

^ Underreported and overall proportion reported and not just prior to breast cancer diagnosis

** These indices were calculated using macro provided by SEER Medicare (Klabundke's modification of Charlson's comorbidity index and NCI comorbidity index). Charlson's comorbidity index is calculated using 7 years prior to breast cancer diagnosis utilized. NCI comorbidity index is calculated using 1 year prior to breast cancer diagnosis utilized.

Table 2: Multivariable cause specific hazards ratio of new onset atrial fibrillation by cancer specific variables in women with breast cancer. Univariable analysis presented in supplemental table 1 was utilized in model building. All variables are adjusted for age, race, ethnicity, marital status, poverty level, urban location status, geographic SEER location, NCI comorbidity index, obesity, smoking, history of hypertension, history of depression, history of anemia and history of stroke. Lymph node biopsy status had greater than 10% missingness and was not modelled for. HER2 status and type of breast cancer only included breast cancer patients after 2010.

Variable	**HR 0 – 90 days after cancer diagnosis (95% CI)**	**HR 91 – 180 days after cancer diagnosis (95% CI)**	**HR > 180 days after cancer diagnosis (95% CI)**
SEER stage			
I (localized)	ref	ref	ref
II (regional direct extension)	2.52 (1.98 – 3.21)	1.55 (1.05 – 2.27)	1.69 (1.24 – 2.30)
III (regional lymph node extension only)	1.50 (1.29 – 1.75)	1.55 (1.28 – 1.88)	1.48 (1.26 – 1.73)
IV (regional direct and lymph node extension)	2.91 (2.35 – 3.61)	2.65 (1.98 – 3.53)	1.93 (1.47 – 2.53)
VII (distant)	4.70 (4.04 – 5.48)	3.48 (2.75 – 4.40)	2.20 (1.72 – 2.83)
Surgical therapy			
No surgery	ref	ref	ref
Localized therapy such as lumpectomy	0.22 (0.19 – 0.25)	0.33 (0.27 – 0.41)	0.55 (0.45 – 0.67)
Total simple mastectomy	0.34 (0.28 – 0.52)	0.40 (0.31 – 0.52)	0.67 (0.53 – 0.86)
Modified radical mastectomy	0.46 (0.38 – 0.53)	0.57 (0.45 – 0.74)	0.75 (0.59 – 0.95)

Variable	**Hazard Ratio***
Laterality – left vs. right	0.95 (0.89 – 1.02)
Grade	
1	ref
2	1.31 (1.18 – 1.46)
3	1.92 (1.72 – 2.15)
4	1.64 (0.98 – 2.76)
AJCC stage	
I	ref
II	1.51 (1.37 – 1.65)
III	2.63 (2.35 – 2.94)
IV	4.21 (3.74 – 4.74)
Radiation therapy	
No radiotherapy	ref
Beam radiation	0.66 (0.61 – 0.72)
Implanted radiation	0.34 (0.24 – 0.46)
Tumor Estrogen Receptor Status vs not	0.66 (0.60 – 0.73)

Tumor Progesterone Receptor Status vs not	0.72 (0.66 – 0.78)
Tumor human epidermal growth factor receptor (HER) 2 Status vs not	1.37 (1.19 – 1.58)
Breast tumor subtype based on combination receptor status	
HER2+/hormone receptor (HR)+	ref
HER2+/HR-	1.26 (0.95 – 1.66)
HER2-/HR+	0.75 (0.63 – 0.89)
HER2-/HR-	1.10 (0.89 – 1.36)

* Variables at the latter part of the table meet proportional hazards assumption and presented hazard ratio are for the entire year. 95% CI = 95% confidence interval, HR = hazards ratio.

Table 3: Association of AF with All-Cause Mortality, Cardiovascular Mortality and Cancer-Specific Mortality at 1 year after diagnosis of cancer. Results from Cox Proportional Hazards Model.

AF Group and Adjustment model	All-Cause Mortality Hazards Ratio (95% confidence interval	Cardiovascular Mortality Hazards Ratio (95% confidence interval)	Cancer Specific Mortality Hazards Ratio (95% confidence interval)
Breast cancer patients with new AF in first 30 days of breast cancer diagnosis (group 1)			
Model 1 - Unadjusted	7.63 (6.50 – 8.96)	8.99 (6.25 – 12.94)	7.65 (6.20 – 9.43)
Model 2	7.68 (6.55 – 9.01)	8.95 (6.22 – 12.89)	7.71 (6.25 – 9.52)
Model 3	3.52 (2.34 – 5.28)	6.43 (3.17 – 13.01)	2.86 (1.57 – 5.22)
Model 4	3.94 (2.30 – 6.76)	9.16 (3.71 – 22.63)	2.44 (1.07 – 5.58)
Model 5	3.11 (2.06 – 4.68)	5.46 (2.69 – 11.10)	2.65 (1.44 – 4.87)
Model 6	2.20 (1.46 – 3.31)	3.85 (1.89 – 7.84)	1.85 (1.00 – 3.40)
Breast cancer patients with prevalent AF prior to breast cancer diagnosis (group 2)			
Model 1 - Unadjusted	2.26 (2.12 – 2.40)	4.74 (4.17 – 5.40)	1.63 (1.49 – 1.79)
Model 2	2.23 (2.10 – 2.38)	4.76 (4.17 – 5.43)	1.61 (1.47 – 1.76)
Model 3	2.28 (2.00 – 2.60)	3.62 (2.85 – 4.60)	1.58 (1.27 – 1.97)
Model 4	2.20 (1.82 – 2.66)	3.72 (2.63 – 5.26)	1.39 (1.01 – 1.92)
Model 5	1.54 (1.34 – 1.78)	1.90 (1.46 – 2.48)	1.29 (1.02 – 1.65)
Model 6	1.02 (0.88 – 1.18)	1.27 (0.97 – 1.67)	0.83 (0.65 – 1.06)

Model 2: model 1 + demographic features; model 3: model 2 + breast cancer related features; model 4: model 3+breast cancer tumor receptor subtype; model 5: model 3 + cardiovascular risk factors for atrial fibrillation; model 6: model 5 + breast cancer medication. Detailed model description presented in supplemental table 2.

Figure 1: Flow chart of study design

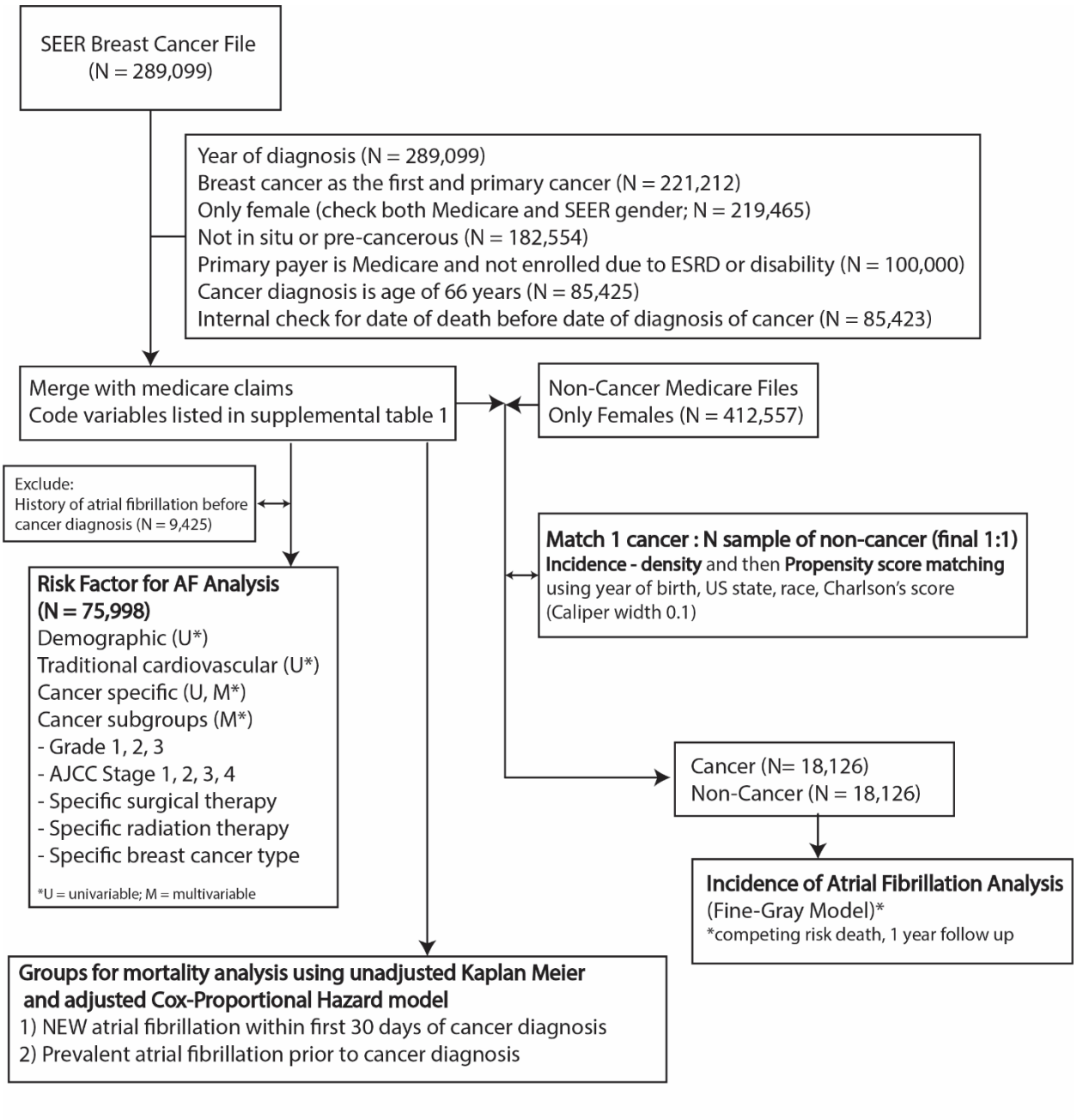


Figure 2: Cumulative incidence function plot for atrial fibrillation in breast cancer patients compared to 1:1 incidence density sampling and propensity matched non-cancer patients. The breast cancer and non-cancer patients were obtained from SEER-Medicare 2007-2014 with matched 5% non-cancer control Medicare sample. Death was a competing risk. Matched for year of birth, race, United States state and Charlson score. Follow-up period of 1-year after cancer diagnosis.

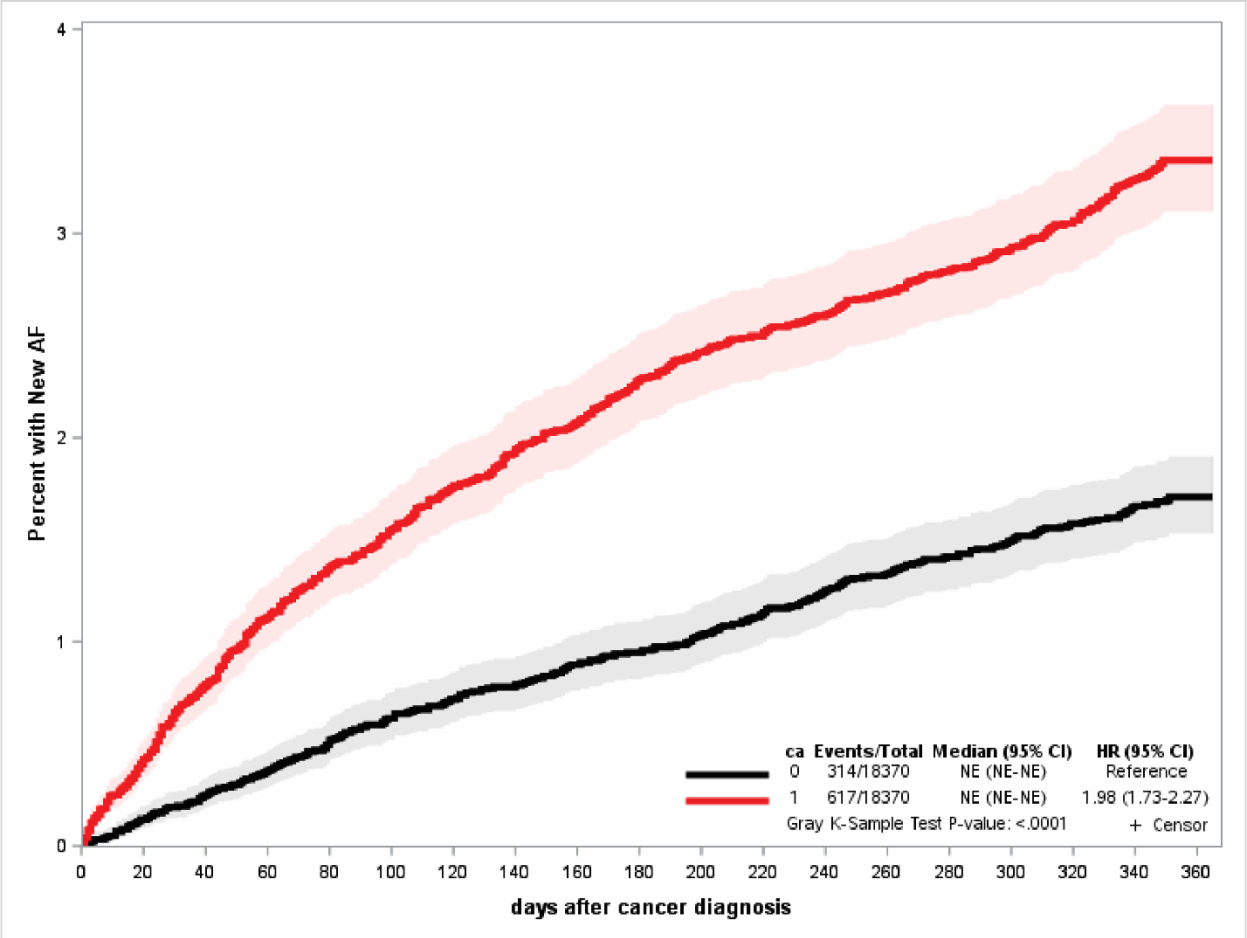


Figure 3: Kaplan Meier all-cause mortality plot of in breast cancer patients who developed AF within 30-days of breast cancer diagnosis compared to those who did not in a 1-year follow-up (A, unadjusted; B, adjusted). The plot is adjusted for standard demographic features, breast cancer related features, cardiovascular risk factors for atrial fibrillation and breast cancer medication. Detailed model description presented in supplemental table 2.

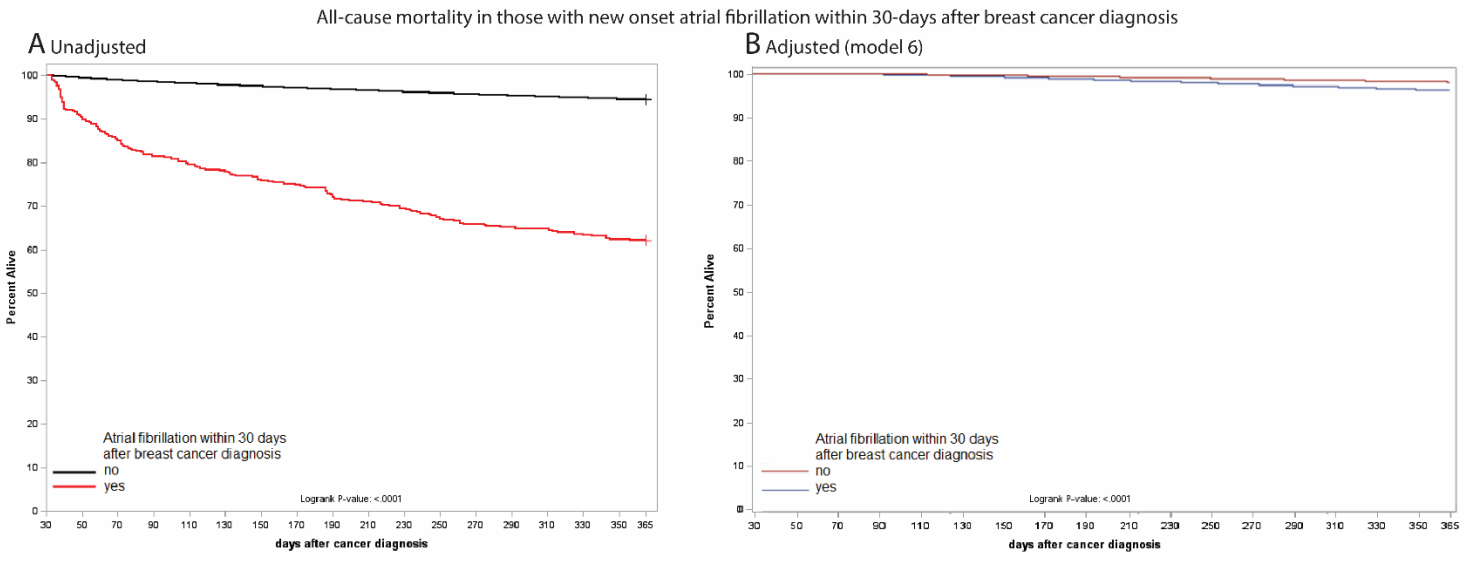
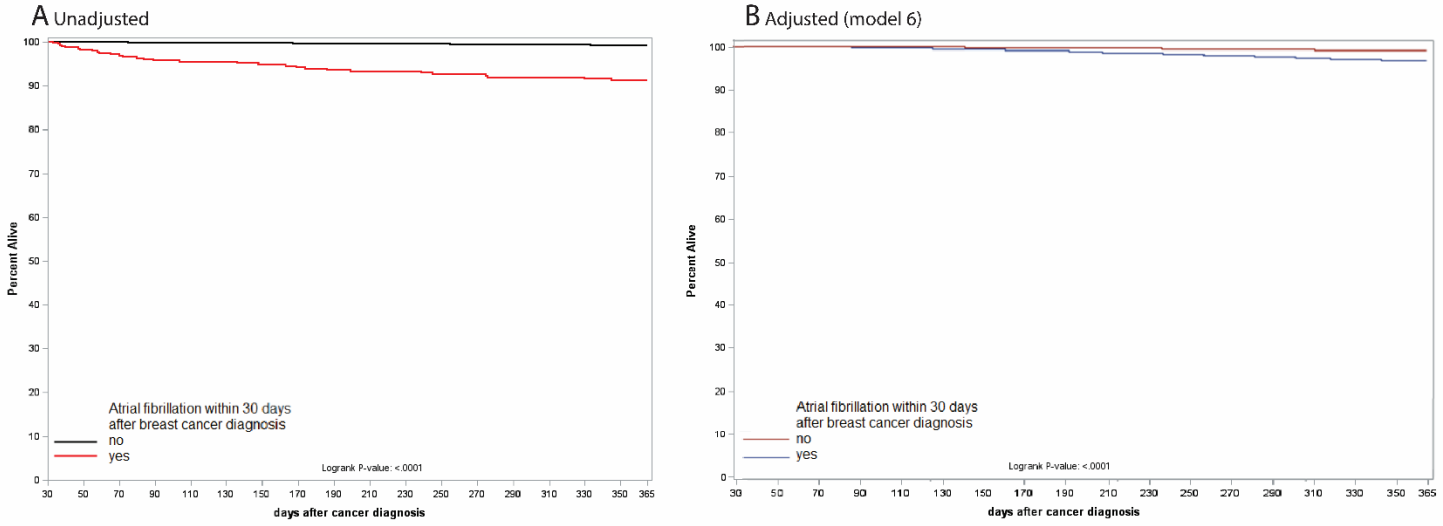
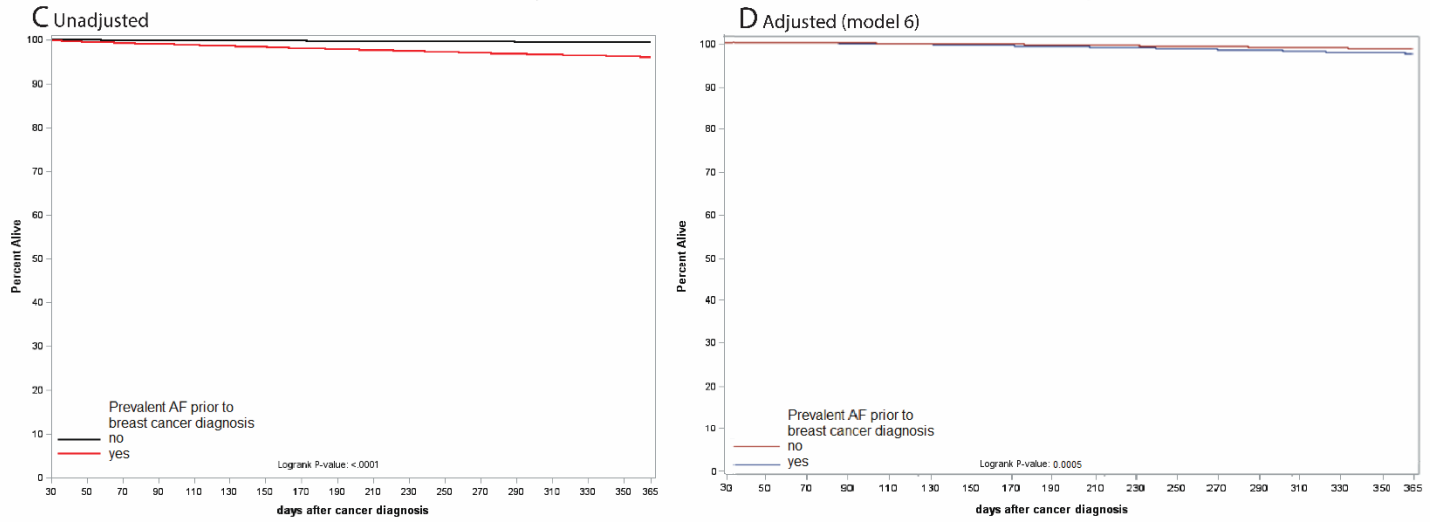


Figure 4 A and B: Kaplan Meier cardiovascular mortality plot of in breast cancer patients who developed AF within 30-days of breast cancer diagnosis compared to those who did not in a 1-year follow-up (A, unadjusted; B, adjusted). **4 C and D:** Kaplan Meier cardiovascular mortality plot of in breast cancer patients who had prevalent AF prior to breast cancer diagnosis compared to those who did not in a 1-year follow-up (C, unadjusted; D, adjusted). The plot is adjusted for standard demographic features, breast cancer related features, cardiovascular risk factors for atrial fibrillation and breast cancer medication. Detailed model description presented in supplemental table 2.

Cardiovascular mortality in those with new onset atrial fibrillation within 30-days after breast cancer diagnosis



Cardiovascular mortality in those with prevalent atrial fibrillation prior to breast cancer diagnosis



Supplemental Table 1: Explanation of variables, univariable cox regression analysis results, proportional hazards assumption test, and source of data in the SEER-Medicare files

Variable	Explanation of variable	Univariable cause-specific hazard ratio (95% confidence interval) [category]	Schonfeld Residual P-value *	Source of data (variable name)
Age at cancer diagnosis	Study includes only patients from age 66 years and above and the age was stratified as: <70 (reference) >=70 to <80 >=80 to <90 >=90	1.31 (1.18 – 1.46) [>=70 to <80] 2.24 (2.01 – 2.50) [>=80 to <90] 3.62 (3.11 – 4.22) [>=90]	0.32	SEER file – this is calculated subtracting date of cancer diagnosis from date of birth. Since only month and year of events are presented, the date of diagnosis is set at 15. (BIRTHM, BIRTHY, MODX1, YRDX1)
Race	Recoded field with classification as: White (reference) Black Other	1.02 (0.90 – 1.15) [Black] 0.69 (0.57 – 0.82) [Other]	0.41	PEDSF – SEER file (RAC_RECA)
Hispanic	Hispanic ethnicity Non-Hispanic (reference)	0.73 (0.62 – 0.86) [Hispanic]	0.03	PEDSF – SEER file (origrecb)
Registry	SEER registry location of the patient when diagnosed with breast cancer. This is a geographic variable: West (reference, includes San Francisco, Hawaii, New Mexico, Seattle, Utah, San Jose, Los Angeles) Northeast (Connecticut, New Jersey) Midwest (Detroit, Iowa, Kentucky) South (Atlanta, rural Georgia, Louisiana, greater Georgia)	1.24 (1.13 – 1.36) 1.13 (1.02 – 1.25) 0.96 (0.87 – 1.07)	0.04	PEDSF – SEER file – the SEER regions were combined into the four categories (REG1)
Marital Status	Marital Status has the following categories: Unmarried-Single (reference) Married Previously Married Unmarried partnered	0.80 (0.70 – 0.91) [married] 1.14 (1.002 – 1.30) [previously married]	0.97	PEDSF – SEER file – marital status at breast cancer diagnosis (marst1)

		1.02 (0.83 – 1.26) [unmarried-partnered]		
Urban	Urban location of the patient at diagnosis with following categories: Large metro (reference) Small metro Other Urban areas (includes urban and less urban) Rural	0.78 (0.58 – 1.06) [small metro] 0.85 (0.78 – 0.92) [urban] 0.90 (0.80 – 1.01) [rural]	0.02	PEDSF – SEER file – urban location at breast cancer diagnosis (urbrur)
Poverty	Census tract poverty indicator: 0% - < 5% poverty (reference) 5 - <10% poverty 10 - <20% poverty 20 – 100% poverty Patients were not deleted but missingness was not addressed hence patients with missingness were not included in the association analysis	1.09 (0.98 – 1.21) [5 - <10%] 1.07 (0.97 – 1.18) [10 - <20%] 1.06 (0.94 – 1.18) [20 – 100%]	0.44	PEDSF – SEER file – poverty indicator at time of breast cancer diagnosis (census_pov_ind)
Laterality	Breast cancer laterality at diagnosis. Although there are breast cancers which were bilateral at diagnosis for epidemiological and due to the clinical question, we included only those who were marked as either right (reference) or left. Patients were not deleted but missingness was not addressed hence patients with either missingness or other laterality indicator were not included in the association analysis	0.95 (0.89 – 1.02) [left]	0.32	PEDSF – SEER file – laterality of breast cancer at diagnosis (lat1)
Grade	North American Association of Central Cancer Registries (NAACCR) grade at breast cancer diagnosis indicated as: 1 (reference) 2 3 4 Patients were not deleted but missingness was not addressed hence patients with either missingness of grade were not included in the association analysis	1.36 (1.22 – 1.51) [grade 2] 1.95 (1.75 – 2.18) [grade 3] 1.54 (0.90 – 2.61) [grade 4]	0.17	PEDSF – SEER file – grade of breast cancer at diagnosis (grade1)
A_stage	American Joint Committee on Cancer (AJCC) stage at breast cancer diagnosis categorized as: 1 (reference) 2 (includes II, II not otherwise specified, IIA, IIB, IIC)	1.58 (1.44 – 1.73) [stage 2] 2.77 (2.48 – 3.09) [stage 3]	<0.0001††	PEDSF – SEER file – AJCC stage at breast cancer diagnosis (DAJCCSTG1)

	3 (includes III, III not otherwise specified, IIIA, IIIB, IIIC) 4 (includes IV, IV not otherwise specified, IVA, IVB, IVC)	4.40 (3.92 – 4.93) [stage 4]		
S_stage	SEER staging is an extent of disease using a SEER algorithm provided by the NAACCR call for data. Classified as: 1 (reference; localized) 2 (regional direct extension) 3 (regional lymph node extension only) 4 (regional direct and lymph node extension) 7 (distant)	2.54 (2.16 – 2.99) [stage 2] 1.46 (1.33 – 1.60) [stage 3] 2.71 (2.35 – 3.12) [stage 4] 3.72 (3.33 – 4.14) [stage 7]	<0.0001	PEDSF – SEER file –SEER stage at breast cancer diagnosis (DSS00S1)
Surgical therapy	Surgery of the primary site as a part of initial work-up or first course of therapy. These are classified as: 0 (reference; no surgery) 1 (localized therapy such as lumpectomy) 2 (total simple mastectomy) 3 (modified radical mastectomy) Patients were not deleted but missingness was not addressed hence patients with missingness were not included in the association analysis	0.27 (0.25 – 0.30) [localized therapy such as lumpectomy] 0.37 (0.33 – 0.41) [total simple mastectomy] 0.46 (0.41 – 0.51) [modified radical mastectomy]	<0.0001	PEDSF – SEER file – any surgery after breast cancer diagnosis (SXPRIF1)
Lymph node surgery	Scope of regional lymph node surgery includes removal, biopsy or aspiration of regional lymph nodes performed during the initial work-up or first course of therapy. We classified them as: 0 (reference; less than 4 lymph nodes removed) 1 (greater than equal to 4 lymph nodes removed) Patients were not deleted but missingness was not addressed hence patients with either missingness of lymph node status were not included in the association analysis	1.56 (1.42 – 1.70) [greater than equal to 4 lymph node removal]	0.09	PEDSF – SEER file – lymph node surgery after breast cancer diagnosis (SXSCOF1)
Radiation therapy	Indication of method of radiation therapy as part of first course of treatment. Classified as: 0 (reference; no radiotherapy) 1 beam radiation 2 implanted radiation Patients were not deleted but missingness was not addressed hence patients with either missingness or other radiation indicators which do	0.56 (0.52 – 0.61) [beam radiation] 0.29 (0.21 – 0.39) [implanted radiation]	<0.0001††	PEDSF – SEER file – radiation therapy type after breast cancer diagnosis (RAD1)

	not discuss type of therapy were not included in the association analysis			
Tumor Estrogen Receptor Status (ER)	Breast cancer ER status per NAACCR present since 2004. Classified as: 0 (reference; negative) 1 (positive) Patients were not deleted but missingness was not addressed hence patients with either missingness or other ER indicators (borderline, indeterminate or before 1990) and were not included in the association analysis	0.69 (0.63 - 0.76)	0.28	PEDSF – SEER file – ER status of breast cancer (ERSTAT1)
Tumor Progesterone Receptor Status (PR)	Breast cancer PR status per NAACCR present since 2004. Classified as: 0 (reference; negative) 1 (positive) Patients were not deleted but missingness was not addressed hence patients with either missingness or other PR indicators (borderline, indeterminate or before 1990) and were not included in the association analysis	0.73 (0.67 - 0.79)	0.22	PEDSF – SEER file – PR status of breast cancer (PRSTAT1)
Tumor human epidermal growth factor receptor 2 Status (HER2)	Breast cancer HER2 status per NAACCR present since 2010. Classified as: 0 (reference; negative) 1 (positive) Patients were not deleted but missingness was not addressed hence patients with either missingness or other HER2 indicators (borderline, indeterminate or before 2010) and were not included in the association analysis	1.34 (1.17 - 1.54)	0.48	PEDSF – SEER file – PR status of breast cancer (HER2REC1)
Breast tumor subtype based on combination receptor status (BrCa subtype)	Breast cancer subtype per NAACCR present since 2010. Classified as: 0 (reference; HER2+/hormone receptor (HR)+) 1 (HER2+/HR-) 2 (HER2-/HR+) 3 (HER2-/HR- = triple negativity) Patients were not deleted but missingness was not addressed hence patients with either missingness or other indicators (unknown or before 2010) and were not included in the association analysis	1.12 (0.85 - 1.47) 0.74 (0.63 - 0.87) 1.07 (0.87 - 1.31)	0.43	PEDSF – SEER file – breast cancer subtype at diagnosis based on ER/PR/HER2 status of NAACCR recode as above (BRSTSUB1)

Comorbities				
Hypertension	Medicare beneficiaries must have at least one inpatient, SNF, or home health claim, or two Part-B (institutional or non-institutional) claims, with a code in any position during the 1-year reference period. The eight years of data (2007-2014) were included to obtain this. The first documented appearance has to be prior to the cancer diagnosis date. Classified as: 0 (reference; no history of diagnosis or diagnosis after breast cancer diagnosis) 1 (history of diagnosis before the breast cancer diagnosis) Those who did not have this diagnosis (1) were assumed to not have this diagnosis (0)	**1.46 (1.34 - 1.58)**	**0.001**	CMS Chronic Conditions Data Flags (HYPERT, HYPERT_EVER)
Diabetes[†(1)‡(1.34)]	Medicare beneficiaries must have at least one inpatient, SNF, or home health claim, or two Part-B (institutional or non-institutional) claims, with a code in any position during the 2-year reference period. The eight years of data (2007-2014) were included to obtain this. The first documented appearance has to be prior to the cancer diagnosis date. Classified as: 0 (reference; no history of diagnosis or diagnosis after breast cancer diagnosis) 1 (history of diagnosis before the breast cancer diagnosis) Those who did not have this diagnosis (1) were assumed to not have this diagnosis (0)	1.55 (1.44 - 1.67)	0.25	CMS Chronic Conditions Data Flags (DIABETES, DIABETES_EVER)
Obesity	Medicare beneficiaries must have at least one inpatient, or two outpatient claims, with a code in any position. All available inpatient and outpatient claims were merged to the final dataset of breast cancer patients. Classified as: 0 (reference; no history of diagnosis or diagnosis after breast cancer diagnosis) 1 (history of diagnosis before the breast cancer diagnosis) Those who did not have this diagnosis (1) were assumed to not have this diagnosis (0)	2.49 (2.18– 2.85)	0.003[††]	Secondary variable created using methodology as described.

History of atrial fibrillation (AF_HX)	NOT included in association analysis as those with prior history of AF_HX were not considered to have new onset AF and not included in the analysis (a-priori exclusion). Those with prior AF are at the highest risk of recurrence and hence not included in the analysis			Modified version of the NCI macro used to calculate index, CMS Chronic Conditions Data Flags (ATRIAL_FIB, ATRIAL_FIB_EVER; beneficiaries must have at least one inpatient claim or two Part-B institutional or non-institutional (carrier) claims with a code in the first or second position during the 1-year reference period). Those who had any AF prior to breast cancer diagnosis were not included in the analysis.
History of ischemic stroke/Transient ischemic attack[†(1)‡(1.32)]	Medicare beneficiaries must have at least one inpatient, SNF, or home health claim, or two Part-B (institutional or non-institutional) claims, with a code in any position during the 1-year reference period. The eight years of data (2007-2014) were included to obtain this. The first documented appearance has to be prior to the cancer diagnosis date. Classified as: 0 (reference; no history of diagnosis or diagnosis after breast cancer diagnosis) 1 (history of diagnosis before the breast cancer diagnosis) Those who did not have this diagnosis (1) were assumed to not have this diagnosis (0)	1.70 (1.53 - 1.88)	0.004	CMS Chronic Conditions Data Flags (STROKE_TIA, STROKE_TIA_EVER)
Hyperlipidemia	Medicare beneficiaries must have at least one inpatient, SNF, or home health claim, or two Part-B (institutional or non-institutional) claims, with a code in any position during the 1-year reference period. The eight years of data (2007-2014) were included to obtain this. The first documented appearance has to be prior to the cancer diagnosis date. Classified as:	1.05 (0.97 - 1.13)	0.0001	CMS Chronic Conditions Data Flags (HYPERL, HYPERL_EVER)

	0 (reference; no history of diagnosis or diagnosis after breast cancer diagnosis) 1 (history of diagnosis before the breast cancer diagnosis) Those who did not have this diagnosis (1) were assumed to not have this diagnosis (0)			
History of congestive heart failure†(1)‡(1.91)	Medicare beneficiaries must have at least one inpatient, or Part-B (institutional or non-institutional) claims, with a code in any position during the 2-year reference period. The eight years of data (2007-2014) were included to obtain this. The first documented appearance has to be prior to the cancer diagnosis date. Classified as: 0 (reference; no history of diagnosis or diagnosis after breast cancer diagnosis) 1 (history of diagnosis before the breast cancer diagnosis) Those who did not have this diagnosis (1) were assumed to not have this diagnosis (0)	2.43 (2.25 – 2.62)	0.004††	CMS Chronic Conditions Data Flags (CHF, CHF_EVER)
History of myocardial infarction†(1)‡(1.08)§	Medicare beneficiaries must have at least one inpatient code in the first or second position during the 1- year reference period. The eight years of data (2007-2014) were included to obtain this. The first documented appearance has to be prior to the cancer diagnosis date. Classified as: 0 (reference; no history of diagnosis or diagnosis after breast cancer diagnosis) 1 (history of diagnosis before the breast cancer diagnosis) Those who did not have this diagnosis (1) were assumed to not have this diagnosis (0)	2.31 (1.93 - 2.77)	0.41	CMS Chronic Conditions Data Flags (AMI, AMI_EVER)
History of ischemic heart disease	Medicare beneficiaries must have at least one inpatient, SNF, home health, or Part-B (institutional or non-institutional) claims, with a code in any position during the 2-year reference period. The eight years of data (2007-2014) were included to obtain this. The first documented appearance has to be prior to the cancer diagnosis date. Classified as: 0 (reference; no history of diagnosis or diagnosis after breast cancer diagnosis) 1 (history of diagnosis before the breast cancer diagnosis)	1.73 (1.61 – 1.86)	0.013	CMS Chronic Conditions Data Flags (ISCHEMICHEART, ISCHEMICHEART_EVER)

	Those who did not have this diagnosis (1) were assumed to not have this diagnosis (0).			
History of lung disease†(1)‡(1.69) #	Medicare beneficiaries must have at least one inpatient, SNF, or home health claim, or two Part-B (institutional or non-institutional) claims, with a code in any position during the 1-year reference period. The eight years of data (2007-2014) were included to obtain this. The first documented appearance has to be prior to the cancer diagnosis date. Classified as: 0 (reference; no history of diagnosis or diagnosis after breast cancer diagnosis) 1 (history of diagnosis before the breast cancer diagnosis) Those who did not have this diagnosis (1) were assumed to not have this diagnosis (0). Includes chronic obstructive pulmonary disease and bronchiectasis.	1.62 (1.49 -1.77)	<0.0001	CMS Chronic Conditions Data Flags (COPD, COPD_EVER)
Smoking	Medicare beneficiaries must have at least one inpatient, or two outpatient claims, with a code in any position. All available inpatient and outpatient claims were merged to the final dataset of breast cancer patients. Classified as: 0 (reference; no history of diagnosis or diagnosis after breast cancer diagnosis) 1 (history of diagnosis before the breast cancer diagnosis) Those who did not have this diagnosis (1) were assumed to not have this diagnosis (0)	**2.05 (1.84 – 2.28)**	**0.004**	Secondary variable created using methodology as described.
Peripheral vascular disease†(1)‡(1.30) **	Medicare beneficiaries must have at least one inpatient, or one outpatient claims, with a code in any position. All available inpatient and outpatient claims were merged to the final dataset of breast cancer patients. The first documented appearance has to be prior to the cancer diagnosis date. Classified as: 0 (reference; no history of diagnosis or diagnosis after breast cancer diagnosis) 1 (history of diagnosis before the breast cancer diagnosis) Those who did not have this diagnosis (1) were assumed to not have this diagnosis (0)	2.04 (1.77 – 2.35)	0.05	Identified using the comorbidity macro as described. This is a secondary variable.

Rheumatological diseases†(1)‡(1.25)	Medicare beneficiaries must have at least two inpatient, SNF, home health, or Part B (institutional or noninstitutional) claims that are at least one day apart with a code in any position during the 2-year reference period. The eight years of data (2007-2014) were included to obtain this. The first documented appearance has to be prior to the cancer diagnosis date. Classified as: 0 (reference; no history of diagnosis or diagnosis after breast cancer diagnosis) 1 (history of diagnosis before the breast cancer diagnosis) Those who did not have this diagnosis (1) were assumed to not have this diagnosis (0). Includes rheumatoid arthritis and osteoarthritis.	1.22 (1.13 - 1.31)	<0.0001	CMS Chronic Conditions Data Flags (RA_OA, RA_OA_EVER)
Alzheimer's dementia†(1)‡(2.06)	Medicare beneficiaries must have at least one inpatient, SNF, home health, Part B institutional, or Part B non-institutional (carrier) claim with an Alzheimer's code in any position during the 3-year reference period. The eight years of data (2007-2014) were included to obtain this. The first documented appearance has to be prior to the cancer diagnosis date. Classified as: 0 (reference; no history of diagnosis or diagnosis after breast cancer diagnosis) 1 (history of diagnosis before the breast cancer diagnosis) Those who did not have this diagnosis (1) were assumed to not have this diagnosis (0).	1.77 (1.59 - 1.96)	0.68	CMS Chronic Conditions Data Flags (ALZH, ALZH _EVER)
History of depression	Medicare beneficiaries must have at least one inpatient, SNF, home health, or Part B (institutional or non-institutional), with a code in any position during the 1-year reference period. All available inpatient and outpatient claims were merged to the final dataset of breast cancer patients. The first documented appearance has to be prior to the cancer diagnosis date. Classified as: 0 (reference; no history of diagnosis or diagnosis after breast cancer diagnosis) 1 (history of diagnosis before the breast cancer diagnosis)	**1.21 (1.12 - 1.32)**	**0.002**	CMS Chronic Conditions Data Flags (DEPR, DEPR _EVER)

	Those who did not have this diagnosis (1) were assumed to not have this diagnosis (0)			
Paralysis†(2)‡(1.49)**	Medicare beneficiaries must have at least one inpatient, or one outpatient claims, with a code in any position. All available inpatient and outpatient claims were merged to the final dataset of breast cancer patients. The first documented appearance has to be prior to the cancer diagnosis date. Classified as: 0 (reference; no history of diagnosis or diagnosis after breast cancer diagnosis) 1 (history of diagnosis before the breast cancer diagnosis) Those who did not have this diagnosis (1) were assumed to not have this diagnosis (0)	1.91 (1.24 - 2.93)	0.15	Identified using the comorbidity macro as described. This is a secondary variable.
Chronic kidney disease†(2)‡(1.60)	Medicare beneficiaries must have at least one inpatient, SNF, or home health claim, or two Part-B (institutional or non-institutional) claims, with a code in any position during the 2-year reference period. The eight years of data (2007-2014) were included to obtain this. The first documented appearance has to be prior to the cancer diagnosis date. Classified as: 0 (reference; no history of diagnosis or diagnosis after breast cancer diagnosis) 1 (history of diagnosis before the breast cancer diagnosis) Those who did not have this diagnosis (1) were assumed to not have this diagnosis (0)	1.84 (1.67 – 2.02)	0.052	CMS Chronic Conditions Data Flags (CHRONICKIDNEY, CHRONICKIDNEY_EVER)
History of anemia	Medicare beneficiaries must have at least one inpatient, SNF, home health, or Part B (institutional or non-institutional), with a code in any position during the 1-year reference period. All available inpatient and outpatient claims were merged to the final dataset of breast cancer patients. The first documented appearance has to be prior to the cancer diagnosis date. Classified as: 0 (reference; no history of diagnosis or diagnosis after breast cancer diagnosis) 1 (history of diagnosis before the breast cancer diagnosis)	**1.46 (1.36 – 1.57)**	**0.003**	CMS Chronic Conditions Data Flags (ANEMIA, ANEMIA_EVER)

	Those who did not have this diagnosis (1) were assumed to not have this diagnosis (0)			
History of Liver disease†(3)‡(2.09)**	Medicare beneficiaries must have at least one inpatient, or one outpatient claims, with a code in any position. All available inpatient and outpatient claims were merged to the final dataset of breast cancer patients. The first documented appearance has to be prior to the cancer diagnosis date. Classified as: 0 (reference; no history of diagnosis or diagnosis after breast cancer diagnosis) 1 (history of diagnosis before the breast cancer diagnosis) Those who did not have this diagnosis (1) were assumed to not have this diagnosis (0)	2.54 (1.21 – 5.34)	0.95	Identified using the comorbidity macro as described. This is a secondary variable.
History of Mild Liver Disease†(1)‡(2.09)**	Medicare beneficiaries must have at least one inpatient, or one outpatient claims, with a code in any position. All available inpatient and outpatient claims were merged to the final dataset of breast cancer patients. The first documented appearance has to be prior to the cancer diagnosis date. Classified as: 0 (reference; no history of diagnosis or diagnosis after breast cancer diagnosis) 1 (history of diagnosis before the breast cancer diagnosis) Those who did not have this diagnosis (1) were assumed to not have this diagnosis (0)	1.55 (0.92 - 2.62)	0.32	Identified using the comorbidity macro as described. This is a secondary variable.
History of Hypothyroidism	Medicare beneficiaries must have at least one inpatient, SNF, or home health claim, or two Part-B (institutional or non-institutional) claims, with a code in any position during the 1-year reference period. The eight years of data (2007-2014) were included to obtain this. The first documented appearance has to be prior to the cancer diagnosis date. Classified as: 0 (reference; no history of diagnosis or diagnosis after breast cancer diagnosis) 1 (history of diagnosis before the breast cancer diagnosis) Those who did not have this diagnosis (1) were assumed to not have this diagnosis (0)	1.08 (0.99 – 1.17)	0.0003	CMS Chronic Conditions Data Flags (HYPOTH, HYPOTH_EVER)

History of gastrointestinal ulcer[†(1)‡(1.08)**]	Medicare beneficiaries must have at least one inpatient, or one outpatient claims, with a code in any position. All available inpatient and outpatient claims were merged to the final dataset of breast cancer patients. The first documented appearance has to be prior to the cancer diagnosis date. Classified as: 0 (reference; no history of diagnosis or diagnosis after breast cancer diagnosis) 1 (history of diagnosis before the breast cancer diagnosis) Those who did not have this diagnosis (1) were assumed to not have this diagnosis (0)	1.47 (0.99 – 2.18)	0.71	Identified using the comorbidity macro as described. This is a secondary variable.
Charlson's comorbidity index[?]	This is the Klabundke's modification that was designed to exclude cancer since all patients in SEER-Medicare have cancer. It includes all variables above with [†] and the (x) next to it has the weights. We utilized all the available data to calculate it (max 7 years of claim for those diagnosed in 2013). We classified this as: 0 (reference) 1 >1	1.30 (1.17 – 1.45) [1] 2.05 (1.87 – 2.26) [>1]	<0.0001	Identified using the comorbidity macro as described. This is a secondary variable.
National Cancer Institute comorbidity index[?]	This is the modification of above by National Cancer Institute statisticians where weights were made specific to various cancers and can also be altered to specific sites (breast, prostate, lung and colorectal cancer). Only data from year prior to cancer diagnosis was used for this. Additionally, the weights were based on [‡]. We classified this as: 0 (reference) >0	**1.84 (1.70 – 2.00)**	**<0.0001**[††]	Identified using the comorbidity macro as described. This is a secondary variable.

* P < 0.05 indicates that variable does not meet proportional hazards assumption for the outcome of atrial fibrillation

[†] These add to the Charlson's comorbidity index and the (x) next to this marker represents the weight in the index

[‡] These add to the NCI comorbidity index and the (x) next to this marker represents the weight in the index

[§] Acute MI also contributes to both comorbidity indices but we present only history of MI as comorbidity here

[#] Indices calculated based only on chronic obstructive pulmonary disease diagnosis and not all lung disease

[**] this covariate when calculated with NCI comorbidity macro using 1 year of claims before breast cancer diagnosis contributes to the NCI comorbidity index, however, the association presented based on 7 years of claims prior to the cancer diagnosis.

[?] These indices were calculated using macro provided by SEER Medicare (Klabundke's modification of Charlson's comorbidity index and NCI comorbidity index). Charlson's comorbidity index is calculated using variable marked using [†], 7 years prior to breast cancer diagnosis utilized, and not used in the model building. NCI comorbidity index is calculated using variables maked using [‡], 1 year prior to breast cancer diagnosis utilized, and is used for model building. This was done to avoid multi-collinearity. AIDS/HIV not included in table above due to very few subjects with that diagnosis but included in comorbidity calculation.

[††] Log-log plots are parallel thus met proportional hazards assumption

Variables included in multivariable analysis. If they are significant then they were included. If they did not meet proportional hazard assumption, then were included as stratifying variables. The variables included in comorbidity were not included again to avoid double counting.

Supplemental Table 2: Adjustment Scheme for Cox-Proportional Hazard Model for Mortality outcome

Model 1	**Model 2**	**Model 3**	**Model 4**	**Model 5**	**Model 6**
Unadjusted	Model 1+	Model 2+	Model 3+	Model 3+	Model 5+
	Age (categorized)	Laterality	Breast tumor subtype based on combination receptor status	Hypertension	Anthracycline vs not
	Race	Grade		Diabetes	Her2inhib vs not
	Hispanic	AJCC stage		Obesity	Cyclophosphamide vs not
	Registry	Surgical therapy		History of ischemic stroke/Transient ischemic attack	Taxanes vs not
	Urban	Lymph node surgery		Hyperlipidemia	Platinum compounds vs not
	Poverty	Radiation therapy		History of congestive heart failure	Hormonal therapy vs not (only who have part D)
				History of myocardial infarction	
				History of lung disease	
				Smoking	
				History of depression	
				History of anemia	

Supplemental Table 3: Incidence of Atrial Fibrillation in the SEER-Medicare in 2007 and 2014

Age at cancer diagnosis (incidence rate per 1000-person years)	Incidence in Medicare 5% sample (2007)*	Incidence in breast cancer patients in SEER-Medicare (2007)	Incidence in breast cancer patients in SEER-Medicare (2014)	Average annual increase
<70	12.9	26.9	32.4	3.4%
>=70 to <80	24.3	31.1	45.9	7.9%
>=80 to <90	45.1	45.3	79.3	12.5%
>=90	68.9	76.9	121.9	9.8%
Race (incidence rate per 1000-person years)				
White	29.4	35.2	49.9	6.0%
Black	22.1	39.8	58.8	6.8%

*adapted from Piccini et al.(1) table 1 and includes males and females whereas breast cancer includes only females. The incidence of AF in females in 2007 was 23.2 per 1000-person years.

Supplemental Table 4: Multivariable cause specific hazards ratio of cancer specific variables modeling for new onset atrial fibrillation in those with breast cancer grade 1, 2, 3. All variables are adjusted for age, race, ethnicity, marital status, poverty level, urban location status, geographic SEER location, NCI comorbidity index, obesity, smoking, history of hypertension, history of depression, history of anemia and history of stroke. HER2 status and type of breast cancer included breast cancer patients after 2010. Surgical therapy does not meet Cox-Proportional Hazards Assumption and 1–90-day risk presented.

Variable	**Hazard Ratio (95% confidence interval) ***			
	Grade 1	**Grade 2**	**Grade 3**	**P-value joint test interaction**
Laterality – left vs. right	0.99 (0.83 – 1.20)	0.99 (0.88 – 1.11)	0.90 (0.79 – 1.03)	0.32
AJCC stage				0.53
I	ref	ref	ref	
II	1.04 (0.82 – 1.32)	1.48 (1.29 – 1.71)	1.46 (1.22 – 1.74)	
III	1.91 (1.28 – 2.86)	2.36 (1.96 – 2.84)	2.37 (1.95 – 2.89)	
IV	2.92 (1.79 – 4.79)	3.60 (2.90 – 4.47)	3.48 (2.75 – 4.40)	
Surgical therapy				0.78
No surgery	ref	ref	ref	
Localized therapy such as lumpectomy	0.38 (0.23 – 0.64)	0.25 (0.19 – 0.33)	0.28 (0.21 – 0.37)	
Total simple mastectomy	0.69 (0.38 – 1.23)	0.35 (0.26 – 0.49)	0.42 (0.30 – 0.59)	
Modified radical mastectomy	0.85 (0.45 – 1.62)	0.52 (0.38 – 0.71)	0.46 (0.34 – 0.63)	
Radiation therapy				0.65
No radiotherapy	ref	ref	ref	
Beam radiation	0.78 (0.63 – 0.96)	0.68 (0.59 – 0.77)	0.71 (0.62 – 0.83)	
Implanted radiation	0.57 (0.34 – 0.95)	0.34 (0.21 – 0.56)	0.32 (0.15 – 0.68)	
Tumor Estrogen Receptor Status vs not	0.76 (0.39 – 1.49)	0.92 (0.74 – 1.16)	0.78 (0.68 – 0.89)	0.74
Tumor Progesterone Receptor Status vs not	1.03 (0.76 – 1.38)	0.82 (0.71 – 0.95)	0.78 (0.68 – 0.89)	0.48
Tumor human epidermal growth factor receptor (HER) 2 Status vs not	1.50 (0.81 – 2.77)	1.43 (1.12 – 1.82)	1.05 (0.86 – 1.29)	0.06
Breast tumor subtype based on combination receptor status				0.30
HER2+/hormone receptor (HR)+	ref	ref	ref	
HER2+/HR-	1.07 (0.13 – 8.86)	0.77 (0.40 – 1.48)	1.45 (1.01 – 2.10)	
HER2-/HR+	0.67 (0.35 – 1.28)	0.67 (0.51 – 0.87)	1.04 (0.79 – 1.37)	

HER2-/HR-	0.56 (0.15 – 2.10)	0.68 (0.44 – 1.06)	1.30 (0.97 – 1.75)	
Anti-Cancer Medication				
Anthracycline vs not	1.36 (0.60 – 3.09)	1.20 (0.85 – 1.71)	0.89 (0.67 – 1.19)	0.75
Her2inhib vs not	0.38 (0.05 – 2.77)	0.92 (0.62 – 1.35)	0.44 (0.32 – 0.60)	0.008
Cyclophosphamide vs not	1.15 (0.61 – 2.18)	0.89 (0.67 – 1.19)	0.82 (0.66 – 1.02)	0.94
Taxanes vs not	1.22 (0.66 – 2.26)	0.98 (0.76 – 1.27)	0.66 (0.53 – 0.81)	0.12
Platinum compounds vs not	NaN	1.16 (0.69 – 1.95)	0.70 (0.49 – 1.02)	0.17
Hormonal therapy vs not	0.15 (0.11 – 0.21)	0.07 (0.05 – 0.08)	0.12 (0.09 – 0.16)	0.01

* includes the first 90 days in case of extended Cox models presented for surgery that did not meet proportional hazards assumption. For standard Cox models follow-up end at 1 year.

Her2inhib = human epidermal growth factor receptor 2 inhibitor; NaN = cannot be presented due to very low sample size

Supplemental Table 5: Multivariable cause specific hazards ratio of cancer specific variables modeling for new onset atrial fibrillation in those with breast cancer AJCC stage 1, 2, 3, 4. All variables are adjusted for age, race, ethnicity, marital status, poverty level, urban location status, geographic SEER location, NCI comorbidity index, obesity, smoking, history of hypertension, history of depression, history of anemia and history of stroke. HER2 status and type of breast cancer included breast cancer patients after 2010. Surgical therapy does not meet Cox-Proportional Hazards Assumption and 1–90-day risk presented.

Variable	**Hazard Ratio (95% confidence interval) ***				
	Stage 1	**Stage 2**	**Stage 3**	**Stage 4**	**P-value joint test interaction**
Laterality – left vs. right	0.92 (0.81 – 1.05)	0.96 (0.84 – 1.10)	1.06 (0.87 – 1.28)	0.93 (0.75 – 1.15)	0.73
Grade					0.53
1	ref	ref	ref	ref	
2	1.02 (0.88 – 1.18)	1.45 (1.15 – 1.81)	1.20 (0.78 – 1.83)	1.30 (0.77 – 2.20)	
3	1.38 (1.14 – 1.64)	1.83 (1.45 – 2.30)	1.57 (1.04 – 2.38)	1.55 (0.92 – 2.60)	
4	0.45 (0.06 – 3.26)	1.93 (0.78 – 4.79)	1.20 (0.36 – 4.06)	0.52 (0.07 – 4.04)	
Surgical therapy					0.84
No surgery	ref	ref	ref	ref	
Localized therapy such as lumpectomy	0.39 (0.24 – 0.62)	0.35 (0.25 – 0.50)	0.39 (0.24 – 0.64)	0.32 (0.16 – 0.63)	
Total simple mastectomy	0.43 (0.25 – 0.76)	0.53 (0.36 – 0.78)	0.41 (0.24 – 0.69)	0.65 (0.33 – 1.29)	
Modified radical mastectomy	0.87 (0.48 – 1.57)	0.56 (0.37 – 0.84)	0.40 (0.27 – 0.60)	0.57 (0.34 – 0.95)	
Radiation therapy					0.24
No radiotherapy	ref	ref	ref	ref	
Beam radiation	0.79 (0.69 – 0.91)	0.65 (0.56 – 0.76)	0.75 (0.61 – 0.92)	0.75 (0.58 – 0.96)	
Implanted radiation	0.42 (0.28 – 0.62)	0.90 (0.50 – 1.60)	NaN	NaN	
Tumor Estrogen Receptor Status vs not	0.83 (0.67 – 1.01)	0.71 (0.60 – 0.84)	0.74 (0.60 – 0.92)	0.68 (0.52 – 0.89)	0.63
Tumor Progesterone Receptor Status vs not	0.90 (0.77 – 1.05)	0.70 (0.61 – 0.81)	0.78 (0.64 – 0.95)	0.84 (0.66 – 1.07)	0.12
Tumor human epidermal growth factor receptor (HER) 2 Status vs not	1.44 (1.11 – 1.88)	1.37 (1.08 – 1.72)	1.13 (0.79 – 1.62)	0.99 (0.65 – 1.52)	0.09
Breast tumor subtype based on combination receptor status					0.02

HER2+/hormone receptor (HR)+	ref	ref	ref	ref	
HER2+/HR-	1.06 (0.60 – 1.87)	1.17 (0.73 – 1.85)	0.77 (0.39 – 1.54)	2.10 (0.96 – 4.63)	
HER2-/HR+	0.71 (0.52 – 0.97)	0.75 (0.57 – 0.99)	0.67 (0.44 – 1.04)	1.37 (0.75 – 2.53)	
HER2-/HR-	0.76 (0.49 – 1.17)	0.90 (0.63 – 1.28)	1.46 (0.91 – 2.35)	1.72 (0.84 – 3.54)	
Anti-Cancer Medication					
Anthracycline vs not	1.10 (0.49 – 2.47)	1.03 (0.74 – 1.44)	0.85 (0.62 – 1.17)	0.37 (0.18 – 0.80)	0.15
Her2inhib vs not	0.76 (0.45 – 1.29)	1.18 (0.97 – 1.43)	0.48 (0.30 – 0.75)	0.20 (0.10 – 0.42)	0.041
Cyclophosphamide vs not	0.71 (0.43 – 1.17)	0.84 (0.65 – 1.09)	0.67 (0.50 – 0.90)	0.83 (0.50 – 1.38)	0.49
Taxanes vs not	1.01 (0.68 – 1.50)	0.74 (0.57 – 0.95)	0.45 (0.33 – 0.60)	0.41 (0.28 – 0.58)	0.002
Platinum compounds vs not	1.29 (0.69 – 2.42)	0.78 (0.48 – 1.27)	0.74 (0.44 – 1.24)	0.33 (0.14 – 0.74)	0.15
Hormonal therapy vs not	0.08 (0.06 – 0.11)	0.08 (0.06 – 0.10)	0.07 (0.05 – 0.10)	0.12 (0.08 – 0.17)	0.15

* includes the first 90 days in case of extended Cox models presented for surgery and SEER stage that did not meet proportional hazards assumption. For standard Cox models follow-up end at 1 year.

Her2inhib = human epidermal growth factor receptor 2 inhibitor; NaN = cannot be presented due to very low sample size

Supplemental Table 6: Multivariable cause specific hazards ratio of cancer specific variables modeling for new onset atrial fibrillation in those with breast cancer stratified by type of surgical therapy. All variables are adjusted for age, race, ethnicity, marital status, poverty level, urban location status, geographic SEER location, NCI comorbidity index, obesity, smoking, history of hypertension, history of depression, history of anemia and history of stroke. HER2 status and type of breast cancer included breast cancer patients after 2010.

Variable	**Hazard Ratio (confidence interval)**				
	No surgery	**Localized therapy such as lumpectomy**	**Total simple mastectomy**	**Modified radical mastectomy**	**P-value joint test interaction**
Laterality – left vs. right	1.04 (0.88 – 1.22)	0.93 (0.83 – 1.04)	0.97 (0.80 – 1.18)	0.93 (0.79 – 1.11)	0.76
Grade					0.78
1	ref	ref	ref	ref	
2	1.26 (0.91 – 1.74)	1.23 (1.06 – 1.43)	1.04 (0.79 – 1.36)	1.56 (1.14 – 2.13)	
3	1.57 (1.13 – 2.17)	1.77 (1.51 – 2.08)	1.53 (1.16 – 2.02)	2.02 (1.49 – 2.76)	
4	1.55 (0.54 – 4.45)	0.96 (0.31 – 3.01)	0.85 (0.19 – 3.73)	1.60 (0.57 – 4.47)	
AJCC stage					0.84
I	ref	ref	ref	ref	
II	1.47 (1.02 – 2.10)	1.40 (1.23 – 1.60)	1.48 (1.18 – 1.84)	1.24 (0.95 – 1.61)	
III	2.15 (1.49 – 3.11)	2.45 (1.95 – 3.08)	2.24 (1.64 – 3.06)	1.93 (1.49 – 2.50)	
IV	2.16 (1.56 – 2.98)	2.96 (1.98 – 4.41)	3.25 (1.97 – 5.36)	2.14 (1.41 – 3.25)	
Radiation therapy					<0.001
No radiotherapy	ref	ref	ref	ref	
Beam radiation	0.97 (0.76 – 1.23)	0.66 (0.57 – 0.75)	1.19 (0.88 -1.61)	1.18 (0.96 – 1.46)	
Implanted radiation	NaN	0.39 (0.28 – 0.55)	NaN	1.41 (0.19 – 10.18)	
Tumor Estrogen Receptor Status vs not	0.78 (0.62 – 0.98)	0.76 (0.64 – 0.89)	0.70 (0.55 – 0.89)	0.58 (0.47 – 0.70)	0.32
Tumor Progesterone Receptor Status vs not	0.87 (0.72 – 1.06)	0.81 (0.71 – 0.93)	0.67 (0.55 – 0.83)	0.65 (0.54 – 0.78)	0.11
Tumor human epidermal growth factor receptor (HER) 2 Status vs not	1.26 (0.90 – 1.75)	1.47 (1.17 – 1.85)	1.20 (0.85 – 1.70)	1.06 (0.75 – 1.49)	0.34
Breast tumor subtype based on combination receptor status					0.38
HER2+/hormone receptor (HR)+	ref	ref	ref	ref	

HER2+/HR-	0.99 (0.53 – 1.83)	1.01 (0.62 – 1.64)	0.88 (0.44 – 1.77)	1.54 (0.80 – 2.94)	
HER2-/HR+	0.78 (0.51 – 1.17)	0.67 (0.51 – 0.87)	0.79 (0.51 – 1.20)	0.96 (0.62 – 1.48)	
HER2-/HR-	0.93 (0.55 – 1.58)	0.84 (0.59 – 1.19)	1.02 (0.61 – 1.72)	2.00 (1.22 – 3.28)	
Anti-Cancer Medication					
Anthracycline vs not	0.56 (0.32 – 0.98)	1.30 (0.91 – 1.87)	0.98 (0.53 – 1.82)	1.18 (0.85 – 1.66)	0.24
Her2inhib vs not	0.38 (0.22 – 0.66)	0.85 (0.59 – 1.22)	0.51 (0.25 – 1.04)	0.65 (0.43 – 0.99)	0.12
Cyclophosphamide vs not	1.03 (0.67 – 1.58)	0.88 (0.66 – 1.16)	1.03 (0.67 – 1.57)	1.02 (0.76 – 1.36)	0.72
Taxanes vs not	0.56 (0.41 – 0.77)	0.89 (0.68 – 1.16)	0.72 (0.46 – 1.11)	0.88 (0.67 – 1.15)	0.43
Platinum compounds vs not	0.46 (0.24 – 0.90)	1.44 (0.96 – 2.17)	0.75 (0.33 – 1.70)	0.75 (0.42 – 1.35)	0.04
Hormonal therapy vs not	0.12 (0.09 – 0.16)	0.07 (0.06 – 0.09)	0.11 (0.07 – 0.15)	0.08 (0.06 – 0.11)	0.12

Her2inhib = human epidermal growth factor receptor 2 inhibitor; NaN = cannot be presented due to very low sample size

Supplemental Table 7: Multivariable cause specific hazards ratio of cancer specific variables modeling for new onset atrial fibrillation in those with breast cancer stratified by radiation therapy. All variables are adjusted for age, race, ethnicity, marital status, poverty level, urban location status, geographic SEER location, NCI comorbidity index, obesity, smoking, history of hypertension, history of depression, history of anemia and history of stroke. HER2 status and type of breast cancer included breast cancer patients after 2010. Surgical therapy does not meet Cox-Proportional Hazards Assumption and 1–90-day risk presented.

Variable	**Hazard Ratio (confidence interval) ***		**P-value joint test interaction**
	No radiotherapy	**Beam radiation**	
Laterality – left vs. right	0.94 (0.86 – 1.03)	0.99 (0.87 – 1.13)	0.46
Grade			0.61
1	ref	ref	
2	1.38 (1.20 – 1.60)	1.26 (1.05 – 1.52)	
3	1.87 (1.61 – 2.17)	1.94 (1.60 – 2.36)	
4	1.34 (0.69 – 2.64)	1.79 (0.66 – 4.87)	
AJCC stage			0.39
I	ref	ref	
II	1.52 (1.34 – 1.71)	1.29 (1.09 – 1.52)	
III	2.64 (2.27 – 3.08)	2.58 (2.14 – 3.10)	
IV	3.82 (3.30 – 4.43)	4.15 (3.26 – 5.28)	
Surgical therapy			<0.0001
No surgery	ref	ref	
Localized therapy such as lumpectomy	0.29 (0.24 – 0.35)	0.20 (0.14 – 0.28)	
Total simple mastectomy	0.33 (0.27 – 0.40)	0.35 (0.19 – 0.63)	
Modified radical mastectomy	0.46 (0.38 – 0.55)	0.42 (0.26 – 0.66)	
Tumor Estrogen Receptor Status vs not	0.67 (0.59 – 0.75)	0.70 (0.59 – 0.84)	0.55
Tumor Progesterone Receptor Status vs not	0.72 (0.65 – 0.79)	0.78 (0.67 – 0.91)	0.27
Tumor human epidermal growth factor receptor (HER) 2 Status vs not	1.34 (1.12 – 1.60)	1.28 (0.98 – 1.68)	0.60
Breast tumor subtype based on combination receptor status			0.96

HER2+/hormone receptor (HR)+	ref	ref	
HER2+/HR-	1.24 (0.87 – 1.76)	1.22 (0.72 – 2.09)	
HER2-/HR+	0.77 (0.62 – 0.96)	0.80 (0.58 – 1.11)	
HER2-/HR-	1.10 (0.84 – 1.45)	1.11 (0.74 – 1.66)	
Anti-Cancer Medication			
Anthracycline vs not	1.05 (0.79 – 1.39)	1.23 (0.90 – 1.68)	0.31
Her2inhib vs not	0.69 (0.51 – 0.92)	0.71 (0.48 – 1.05)	0.79
Cyclophosphamide vs not	0.84 (0.67 – 1.06)	1.11 (0.87 – 1.42)	0.07
Taxanes vs not	0.83 (0.68 – 1.01)	0.94 (0.74 – 1.20)	0.34
Platinum compounds vs not	0.80 (0.55 – 1.16)	1.24 (0.80 – 1.92)	0.11
Hormonal therapy vs not	0.11 (0.09 – 0.13)	0.06 (0.05 – 0.08)	0.0006

* includes the first 90 days in case of extended Cox models presented for surgery that did not meet proportional hazards assumption. For standard Cox models follow-up end at 1 year.

Her2inhib = human epidermal growth factor receptor 2 inhibitor

Supplemental Table 8: Multivariable cause specific hazards ratio of cancer specific variables modeling for new onset atrial fibrillation in those with breast cancer subtype based on receptor status. All variables are adjusted for age, race, ethnicity, marital status, poverty level, urban location status, geographic SEER location, NCI comorbidity index, obesity, smoking, history of hypertension, history of depression, history of anemia and history of stroke. The type of breast cancer included breast cancer patients after 2010. Surgical therapy does not meet Cox-Proportional Hazards Assumption and 1–90-day risk presented.

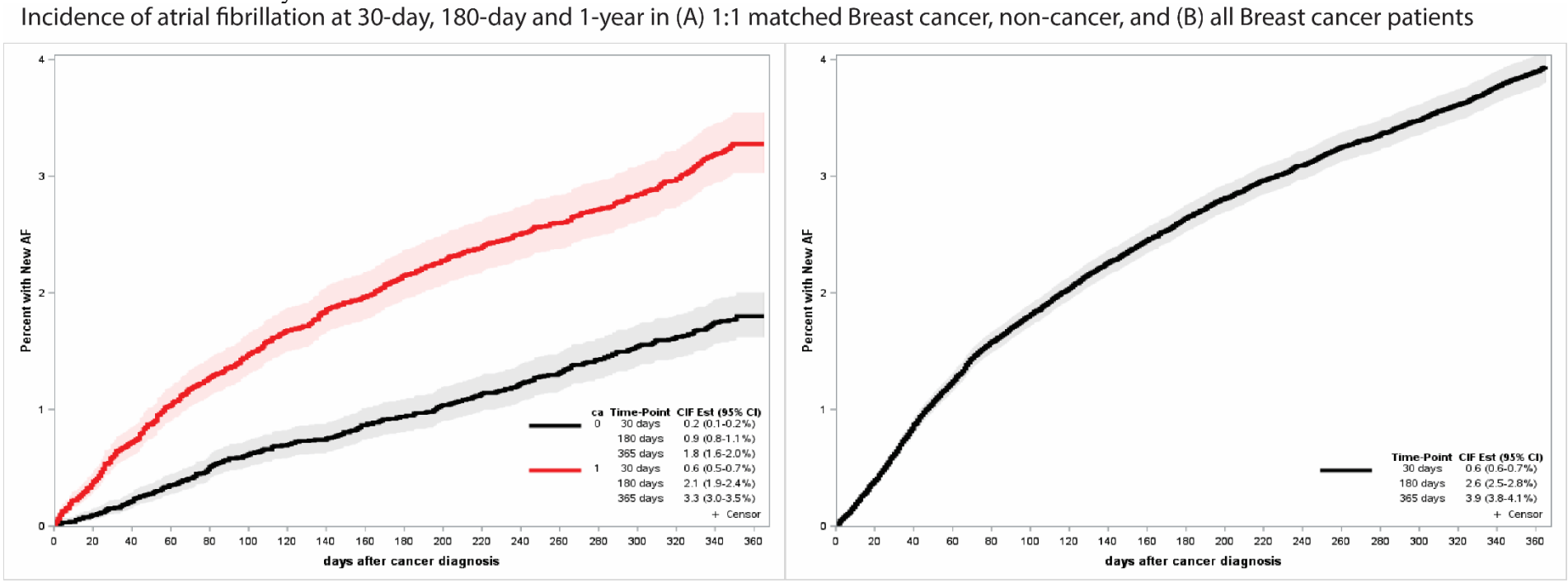
Variable	**Hazard Ratio (confidence interval) ***				**P-value joint test interaction**
	HER2+/hormone receptor (HR)+	**HER2+/HR-**	**HER2-/HR+**	**HER2-/HR-**	
Laterality – left vs. right	1.06 (0.76 – 1.49)	0.86 (0.52 – 1.43)	0.96 (0.86 – 1.08)	1.00 (0.74 – 1.35)	0.97
Grade					0.30
1	ref	ref	ref	ref	
2	1.36 (0.68 – 2.74)	NaN	1.17 (1.02 – 1.36)	1.44 (0.42 – 5.00)	
3	1.03 (0.51 – 2.06)	NaN	1.67 (1.41 – 1.98)	NaN	
4	NaN	NaN	0.65 (0.09 – 4.74)	NaN	
AJCC stage					0.02
I	ref	ref	ref	ref	
II	1.50 (0.99 – 2.26)	1.50 (0.75 – 2.99)	1.50 (1.31 – 1.71)	1.64 (1.09 – 2.47)	
III	1.92 (1.16 – 3.19)	1.34 (0.55 – 3.26)	2.01 (1.66 – 2.43)	3.70 (2.41 – 5.69)	
IV	2.05 (1.10 – 3.84)	4.00 (1.71 – 9.35)	3.68 (3.00 – 4.51)	4.22 (2.44 – 7.30)	
Surgical therapy					0.38
No surgery	ref	ref	ref	ref	
Localized therapy such as lumpectomy	0.20 (0.09 – 0.41)	0.14 (0.04 – 0.47)	0.28 (0.22 – 0.35)	0.22 (0.11 – 0.46)	
Total simple mastectomy	0.34 (0.13 – 0.89)	0.16 (0.03 – 0.76)	0.49 (0.37 – 0.66)	0.45 (0.21 – 0.98)	
Modified radical mastectomy	0.27 (0.10 – 0.71)	0.14 (0.03 – 0.70)	0.59 (0.42 – 0.81)	0.68 (0.35 – 1.30)	
Radiation therapy					0.86
No radiotherapy	ref	ref	ref	ref	
Beam radiation	0.56 (0.37 – 0.83)	0.56 (0.31 – 1.02)	0.69 (0.61 – 0.79)	0.61 (0.44 – 0.85)	
Implanted radiation	1.17 (0.36 – 3.85)	NaN	0.43 (0.28 – 0.65)	0.17 (0.02 – 1.25)	
Anti-Cancer Medication					
Anthracycline vs not	0.91 (0.28 – 2.93)	NaN	1.41 (0.98 – 2.04)	0.96 (0.52 – 1.78)	0.58
Her2inhib vs not	0.39 (0.25 – 0.61)	0.23 (0.12 – 0.46)			

Cyclophosphamide vs not	0.76 (0.30 – 1.93)	0.20 (0.03 – 1.52)	1.07 (0.82 – 1.39)	0.76 (0.48 – 1.18)	0.23
Taxanes vs not	0.66 (0.42 – 1.05)	0.37 (0.18 – 0.77)	1.09 (0.86 – 1.39)	0.66 (0.43 – 1.01)	0.04
Platinum compounds vs not	0.99 (0.58 – 1.72)	0.65 (0.29 – 1.47)	1.07 (0.43 – 2.66)	0.31 (0.07 – 1.31)	0.40
Hormonal therapy vs not	0.05 (0.03 – 0.09)		0.05 (0.04 – 0.07)		

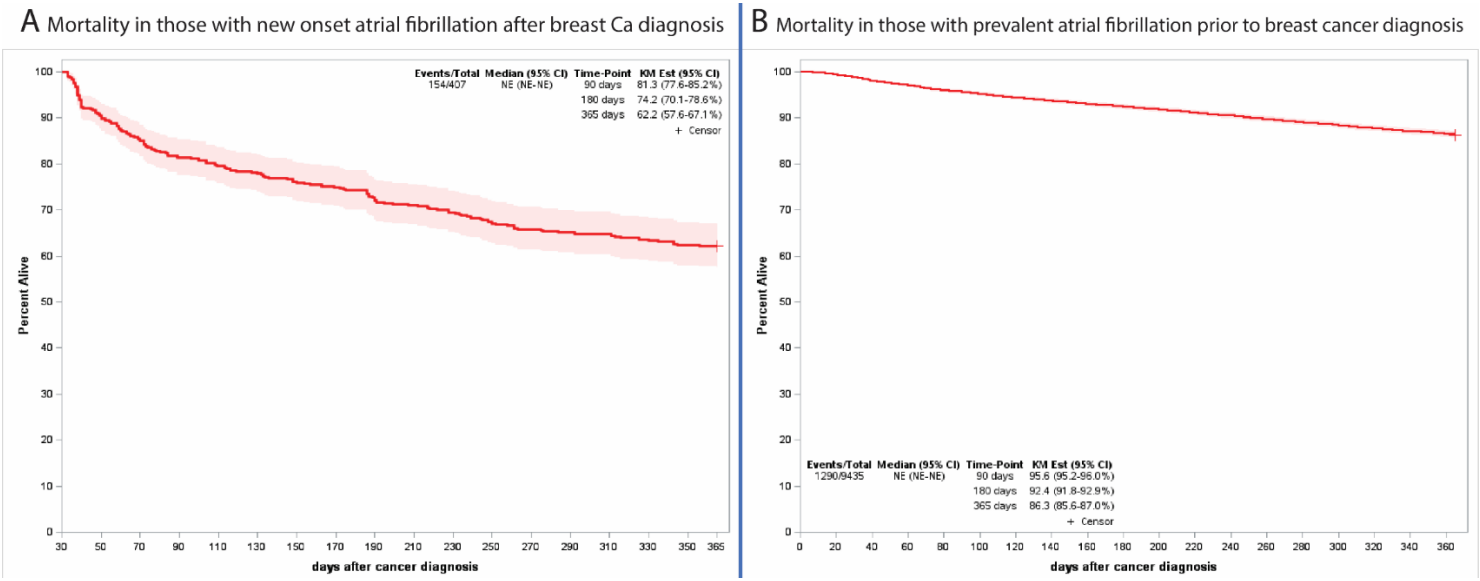
* includes the first 90 days in case of extended Cox models presented for surgery that did not meet proportional hazards assumption. For standard Cox models follow-up end at 1 year.

Her2inhib = human epidermal growth factor receptor 2 inhibitor; NaN = cannot be presented due to very low sample size

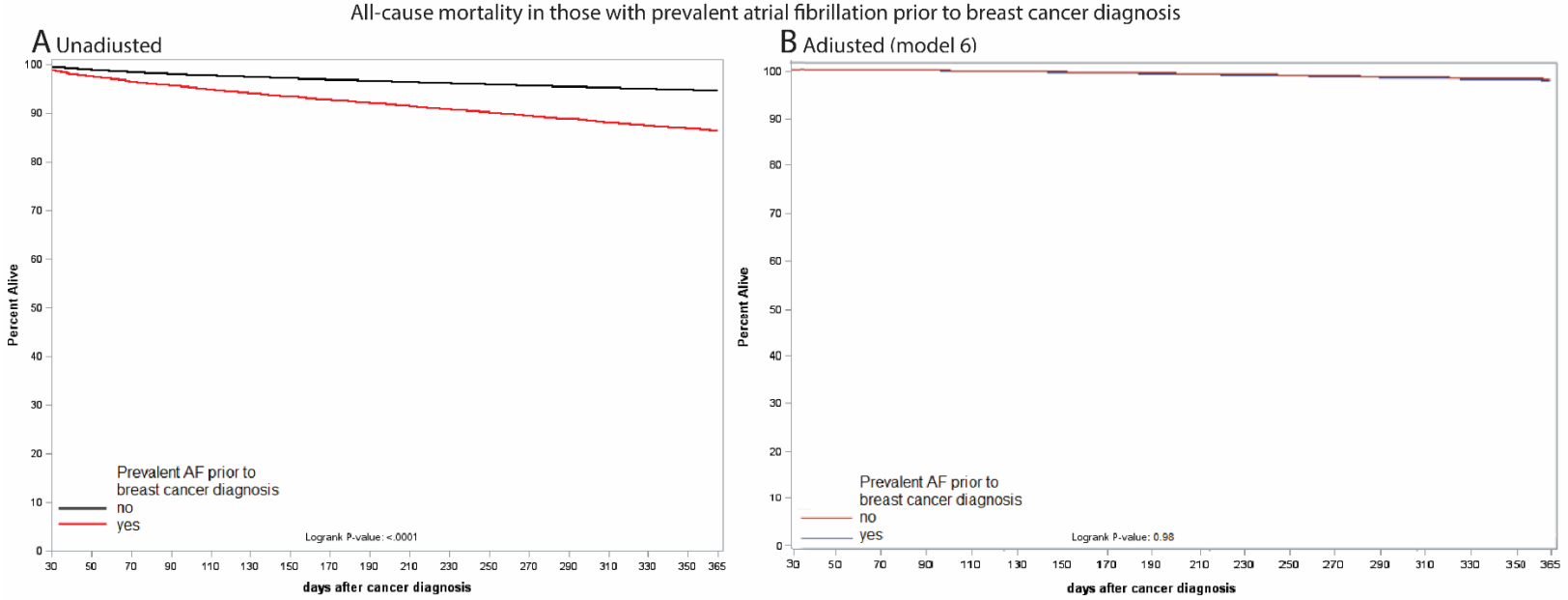
Supplemental figure 1A: Incidence of atrial fibrillation at 30-day, 180-day and 365-day period in a matched sample of breast cancer and non-cancer patients. Patient are matched for year of birth, gender, race (white or nonwhite [black, Asian, Pacific Islander, other]), SEER registry (a surrogate for geographic region categorized into Northeast, South, Midwest, and West regions), and Charlson comorbidity index in the year before study entry (dichotomized into 0 or ≥1). The initial matching is incidence density sampling based matching following which 1:1 matching performed using propensity score matching with a 10% caliper. **(1B)** Incidence of atrial fibrillation 30-day, 180-day and 365-day period in all breast cancer patients after diagnosis of breast cancer. There is higher rate of AF occurrence in the 1st 90 days.



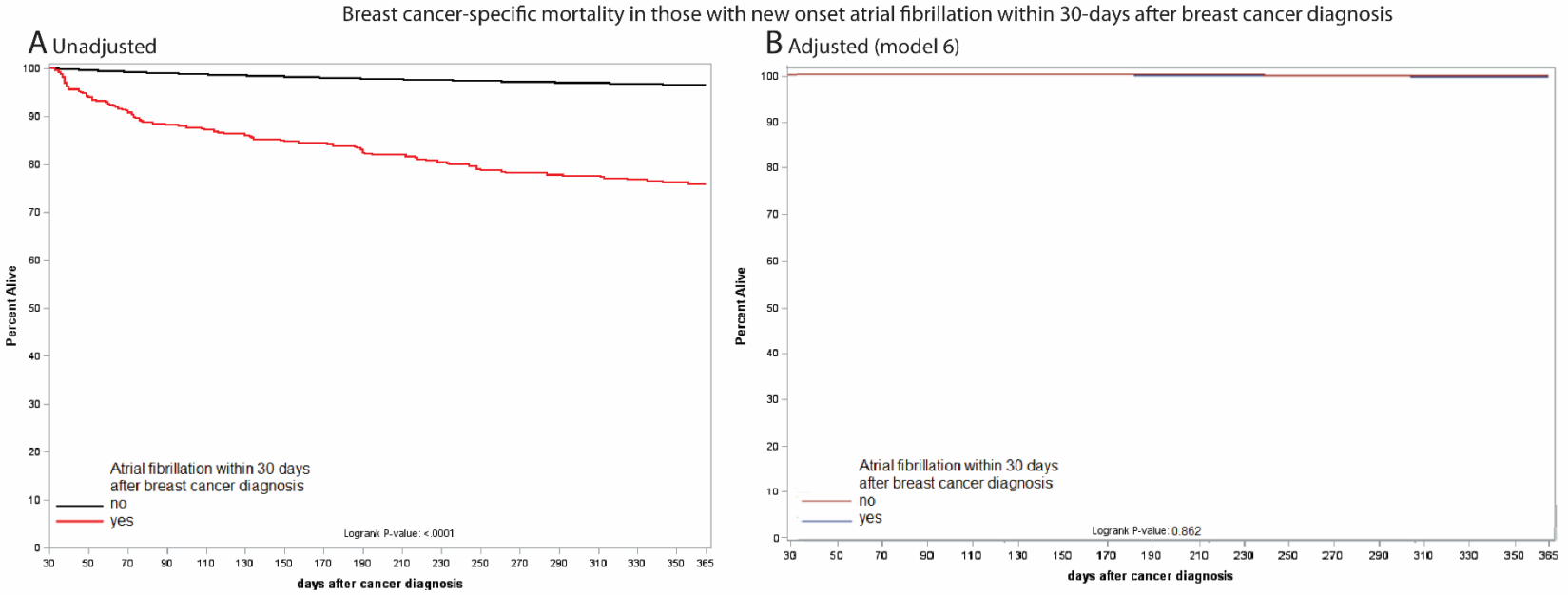
Supplemental figure 2: Kaplan Meier plot of breast cancer patients who developed AF within 30-days of cancer diagnosis (A), and those with AF prior to breast cancer diagnosis (B).



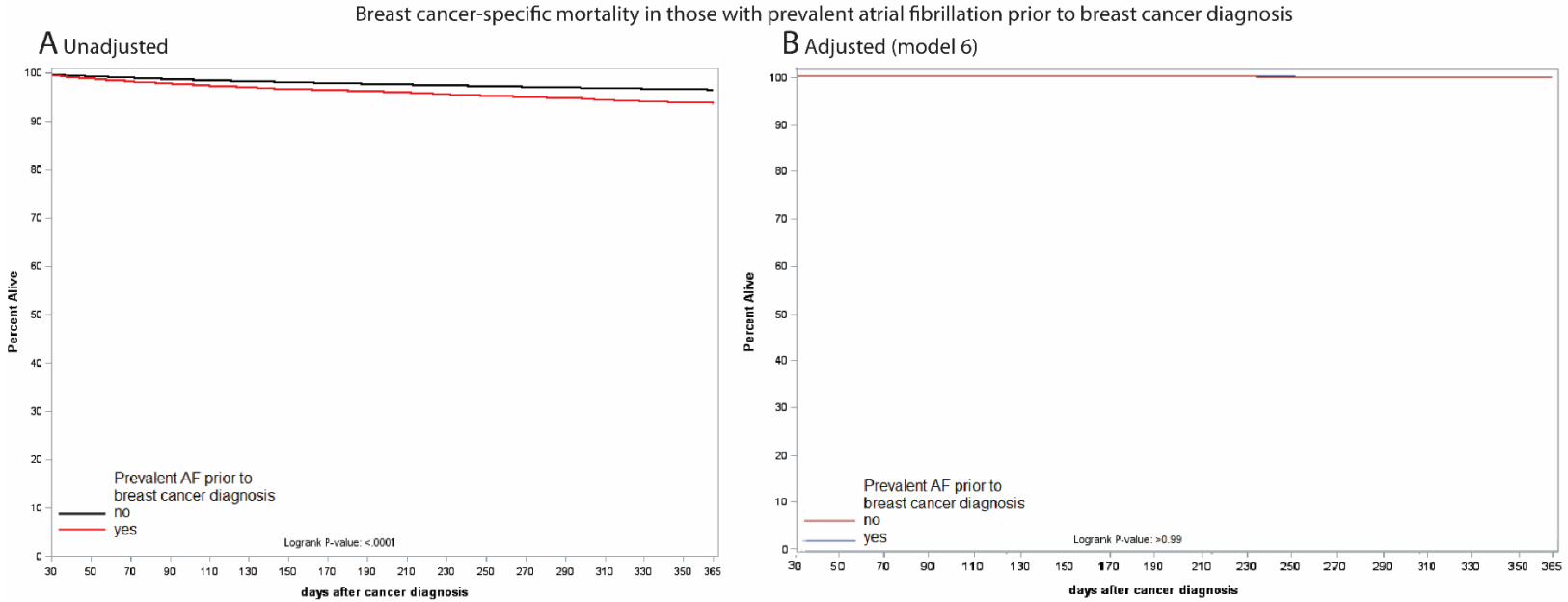
Supplemental figure 3: Kaplan Meier all-cause mortality plot of in breast cancer patients who had prevalent AF prior to breast cancer diagnosis compared to those who did not in a 1-year follow-up (A, unadjusted; B, adjusted). The plot is adjusted for standard demographic features, breast cancer related features, cardiovascular risk factors for atrial fibrillation and breast cancer medication. Detailed model description presented in supplemental table 2.



Supplemental figure 4: Kaplan Meier breast cancer-specific mortality plot of in breast cancer patients who developed AF within 30-days of breast cancer diagnosis compared to those who did not in a 1-year follow-up (A, unadjusted; B, adjusted). The plot is adjusted for standard demographic features, breast cancer related features, cardiovascular risk factors for atrial fibrillation and breast cancer medication. Detailed model description in supplemental table 2.



Supplemental figure 5: Kaplan Meier breast cancer-specific mortality plot of in breast cancer patients who had prevalent AF prior to breast cancer diagnosis compared to those who did not in a 1-year follow-up (A, unadjusted; B, adjusted). The plot is adjusted for standard demographic features, breast cancer related features, cardiovascular risk factors for atrial fibrillation and breast cancer medication. Detailed model description presented in supplemental table 2.



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1. Piccini JP, Hammill BG, Sinner MF, Jensen PN, Hernandez AF, Heckbert SR, Benjamin EJ, Curtis LH. Incidence and prevalence of atrial fibrillation and associated mortality among Medicare beneficiaries, 1993-2007. *Circ Cardiovasc Qual Outcomes*. 2012 Jan;**5**(1):85-93.